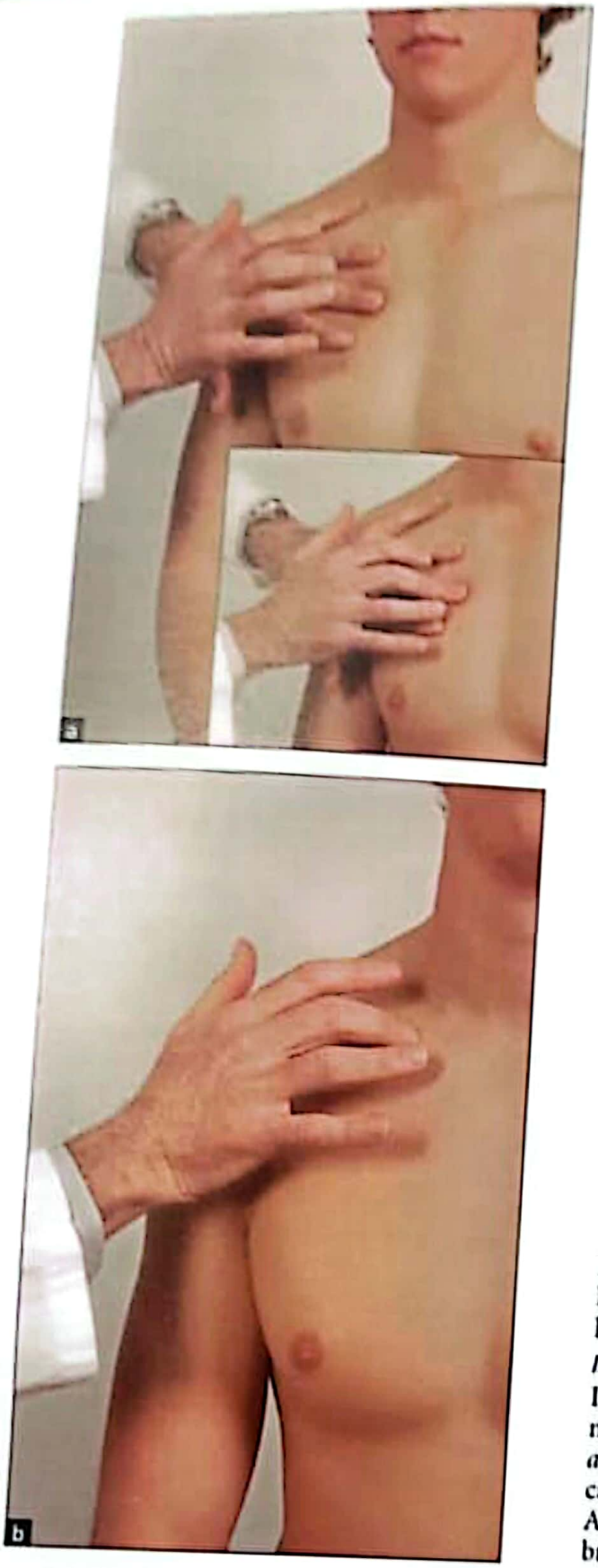

Figure 10.10 Percussion of the chest
(a) Percussing (plexor) finger poised. Inset: plexor finger strikes pleximeter finger. (b) Direct percussion of the clavicle for upper lobe resonance.
(Courtesy of Glenn McCulloch)

A number of observations must be made when auscultating and, as with auscultation of the heart, different parts of the cycle must be considered separately for the quality of the breath sounds, the intensity of the breath sounds and the presence of added (adventitious) sounds.

### Quality of breath sounds

*Normal breath sounds* are heard with the stethoscope over nearly all parts of the chest. The patient should be asked to breathe in and out through the mouth* so that added sounds from the nasopharynx do not interfere.[1] During expiration these sounds are produced in the large airways rather than in the alveoli. However, inspiratory sounds are probably produced closer to where they are heard, in the peripheral parts of the lungs. Since both sounds were once thought to arise in the alveoli, or vesicles of the lungs, they are called vesicular sounds. They have rather fancifully been compared by Laënnec to the sound of wind rustling in leaves. Their intensity is related to total airflow at the mouth and to regional airflow. Normal (vesicular) breath sounds are louder and longer on inspiration than on expiration and there is no gap between the inspiratory and expiratory sounds.

*Bronchial breath sounds* are present when turbulence in the large airways is heard without being filtered by the alveoli. Bronchial breath sounds have a hollow, blowing quality. They are audible throughout expiration and there is often a gap between inspiration and expiration. The expiratory sound has a higher intensity and pitch than the inspiratory sound. Bronchial breath sounds are more easily remembered than described. They are audible in normal people posteriorly over the right upper chest where the trachea is contiguous with the right upper bronchus. They are heard over areas of consolidation, as solid lung conducts the sound of turbulence in main airways to peripheral areas without filtering. Causes of bronchial breath sounds are shown in List 10.3.

Occasionally, breath sounds over a large cavity have an exaggerated bronchial quality. This very hollow or *amphoric*[1] sound has been likened to that heard when air passes over the top of a hollow jar.

### Intensity of the breath sounds

It is better to describe breath sounds as being of normal or reduced intensity than to speak about *air entry*. The entry of air into parts of the lung cannot be directly gauged from the breath sounds. Asymmetrical reduction of breath sounds is a sign of bronchial obstruction, for example by carcinoma or

* Many people when asked to take big breaths, breathe in, and then, for some reason, stop. Although it is tempting to amuse oneself by waiting patiently for the patient to realise that expiration is also a part of breathing, this tends to waste time.

[1] From the Greek *amphiphoreus* meaning a 'vase with a narrow neck'.

# MDR TB Update

Dr Radha Munje
Professor &Head
Respiratory Medicine
IGGMC Nagpur

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# Grouping* of anti-TB drugs and other consideration

| Groups & steps | Medicine | Abbreviation |
|---|---|---|
| Group A<br>Include all three medicines | Levofloxacin or<br>Moxifloxacin | Lfx<br>Mfx |
| | Bedaquiline | Bdq |
| | Linezolid | Lzd |
| Group B<br>Add one or both medicines | Clofazimine | Cfz |
| | Cycloserine or<br>Terizidone | Cs<br>Trd |
| Group C<br>Add to complete the regimen and when medicines from Group A and B cannot be used | Ethambutol | E |
| | Delamanid | Dlm |
| | Pyrazinamide | Z |
| | Imipenem-cilastatin or<br>Meropenem | Ipm-Cln<br>Mpm |
| | Amikacin<br>(OR Streptomycin) | Am<br>(S) |
| | Ethionamide or<br>Prothionamide | Eto<br>Pto |
| | p-aminosalicylic acid | PAS |

* *Reference: WHO Consolidated Guidelines for TB module 4: Treatment of DR-TB 2020*

***Annexure 11: evidences on efficacy and safety of the second-line anti-TB drugs***

## Drugs not included in Groups A–C

- **Kanamycin and Capreomycin:**
  - Associated with poorer outcomes
  - No longer recommended for use in MDR-TB regimens.
- **Gatifloxacin**
  - Non availability of quality-assured preparations due to concern about dysglycaemias.
- **Thioacetazone**
  - Not available in a quality-assured formulation.
- **Clavulanic acid**
  - Only a companion agent to the carbapenems (Imp-Cln and Mpm)
  - Not to be counted as an effective TB agent



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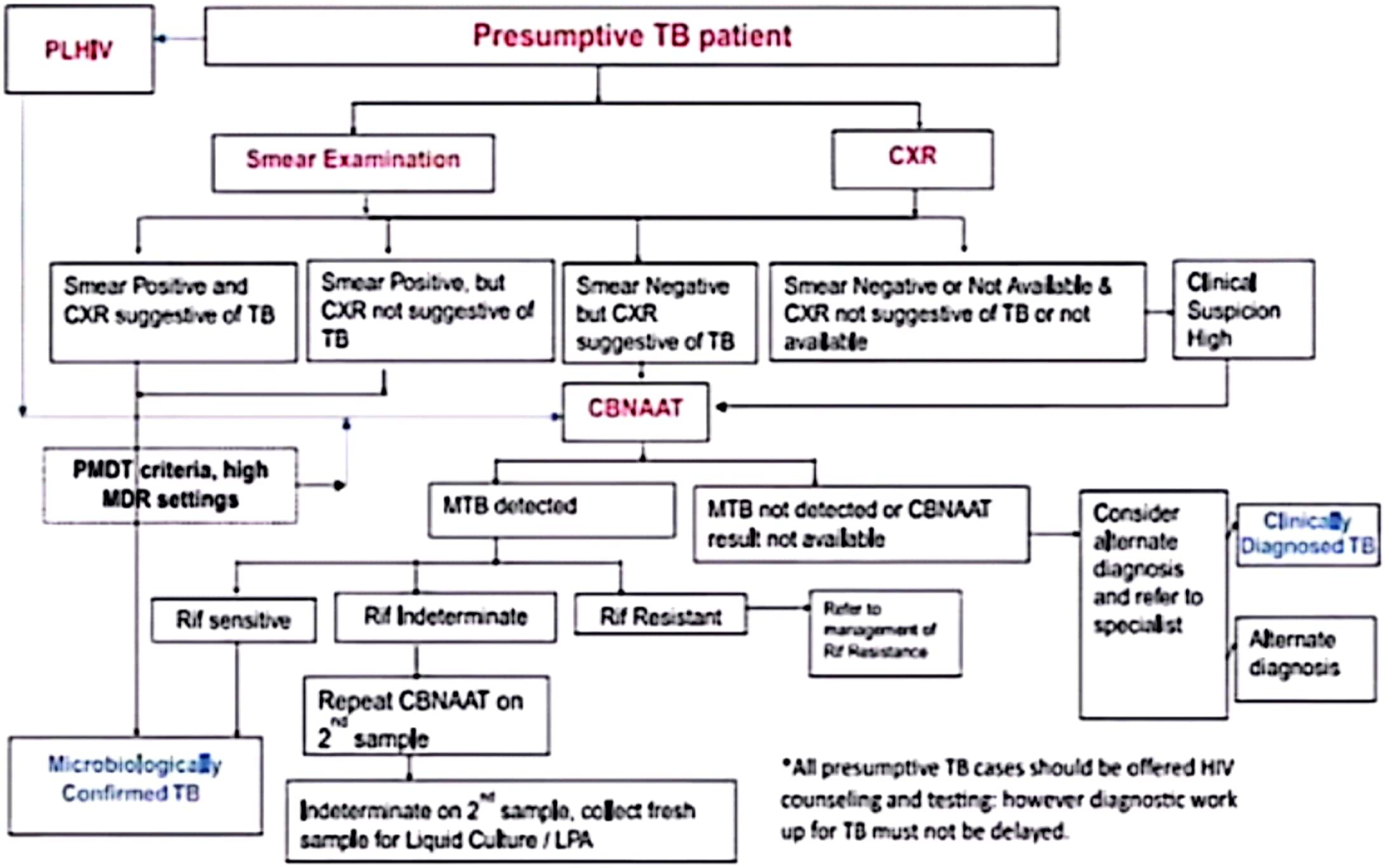
## Diagnostic algorithm for pulmonary TB


PLHIV
Presumptive TB patient
Smear Examination
CXR
Smear Positive and CXR suggestive of TB
Smear Positive, but CXR not suggestive of TB
Smear Negative but CXR suggestive of TB
Smear Negative or Not Available & CXR not suggestive of TB or not available
Clinical Suspicion High
CBNAAT
PMDT criteria, high MDR settings
MTB detected
MTB not detected or CBNAAT result not available
Consider alternate diagnosis and refer to specialist
Clinically Diagnosed TB
Alternate diagnosis
Rif sensitive
Rif Indeterminate
Rif Resistant
Refer to management of Rif Resistance
Repeat CBNAAT on 2nd sample
Microbiologically Confirmed TB
Indeterminate on 2nd sample, collect fresh sample for Liquid Culture / LPA

*All presumptive TB cases should be offered HIV counseling and testing; however diagnostic work up for TB must not be delayed.

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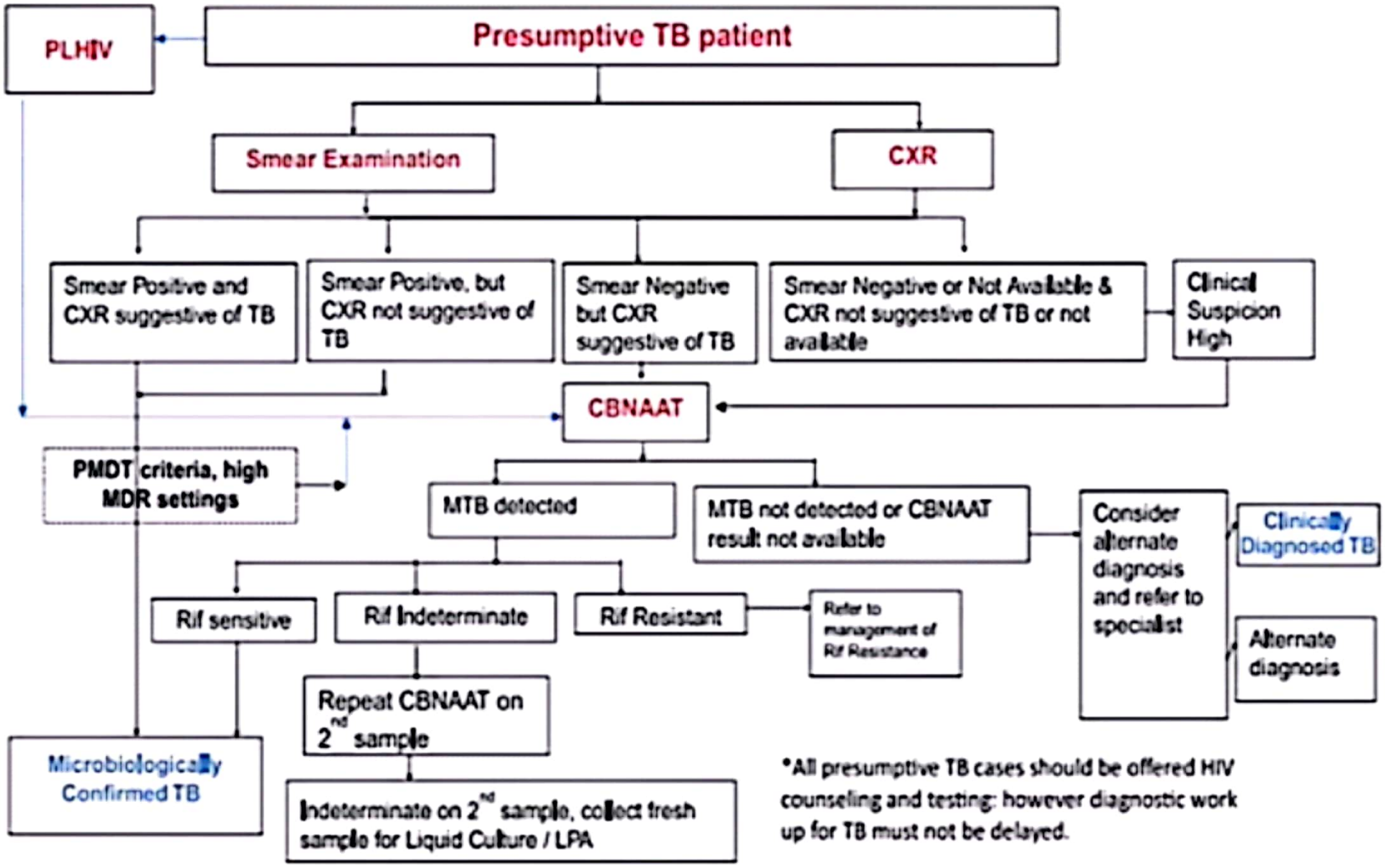
# Diagnostic algorithm for pulmonary TB


PLHIV
Presumptive TB patient
Smear Examination
CXR
Smear Positive and CXR suggestive of TB
Smear Positive, but CXR not suggestive of TB
Smear Negative but CXR suggestive of TB
Smear Negative or Not Available & CXR not suggestive of TB or not available
Clinical Suspicion High
CBNAAT
PMDT criteria, high MDR settings
MTB detected
MTB not detected or CBNAAT result not available
Consider alternate diagnosis and refer to specialist
Clinically Diagnosed TB
Alternate diagnosis
Rif sensitive
Rif Indeterminate
Rif Resistant
Refer to management of Rif Resistance
Repeat CBNAAT on 2nd sample
Microbiologically Confirmed TB
Indeterminate on 2nd sample, collect fresh sample for Liquid Culture / LPA

*All presumptive TB cases should be offered HIV counseling and testing; however diagnostic work up for TB must not be delayed.

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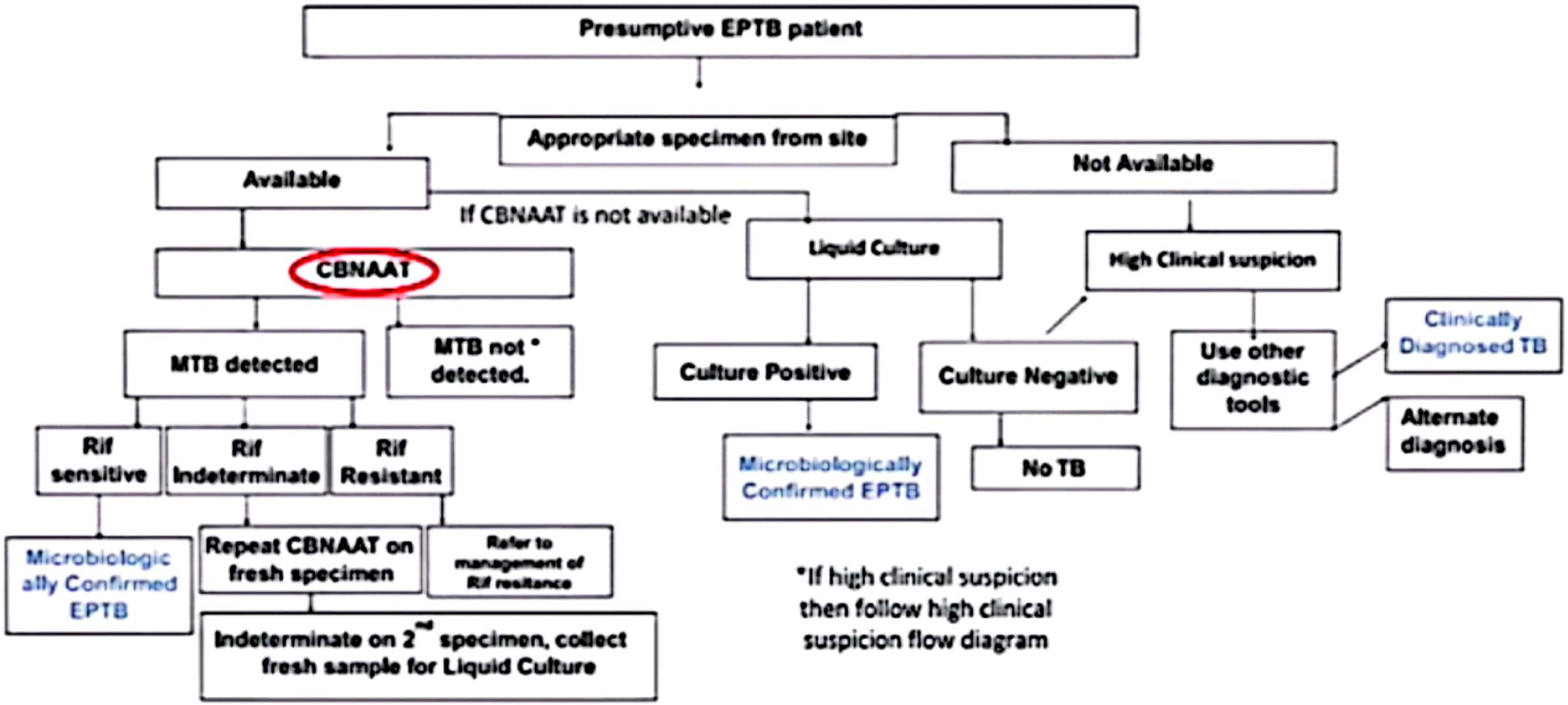
# NTEP EPTB DIAGNOSTIC ALGORITHM

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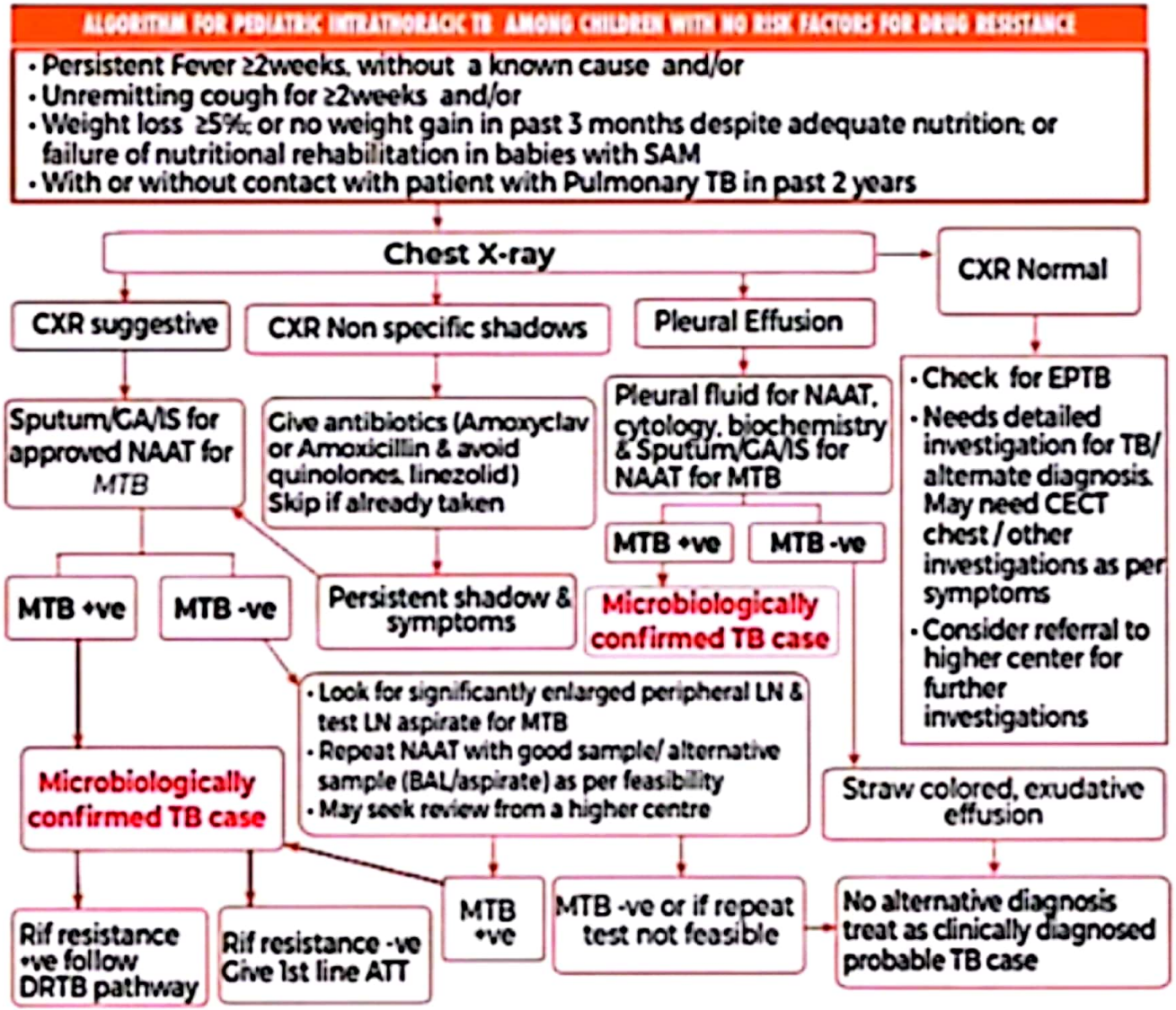
ALGORITHM FOR PEDIATRIC INTRATHORACIC TB AMONG CHILDREN WITH NO RISK FACTORS FOR DRUG RESISTANCE
• Persistent Fever ≥2weeks, without a known cause and/or
• Unremitting cough for ≥2weeks and/or
• Weight loss ≥5% or no weight gain in past 3 months despite adequate nutrition; or failure of nutritional rehabilitation in babies with SAM
• With or without contact with patient with Pulmonary TB in past 2 years
Chest X-ray
CXR Normal
CXR suggestive
CXR Non specific shadows
Pleural Effusion
Sputum/GA/IS for approved NAAT for MTB
Give antibiotics (Amoxyclav or Amoxicillin & avoid quinolones, linezolid) Skip if already taken
Pleural fluid for NAAT, cytology, biochemistry & Sputum/GA/IS for NAAT for MTB
• Check for EPTB
• Needs detailed investigation for TB/ alternate diagnosis. May need CECT chest / other investigations as per symptoms
• Consider referral to higher center for further investigations
MTB +ve
MTB -ve
MTB +ve
MTB -ve
Persistent shadow & symptoms
Microbiologically confirmed TB case
• Look for significantly enlarged peripheral LN & test LN aspirate for MTB
• Repeat NAAT with good sample/ alternative sample (BAL/aspirate) as per feasibility
• May seek review from a higher centre
Microbiologically confirmed TB case
Straw colored, exudative effusion
Rif resistance +ve follow DRTB pathway
Rif resistance -ve Give 1st line ATT
MTB +ve
MTB -ve or if repeat test not feasible
No alternative diagnosis treat as clinically diagnosed probable TB case

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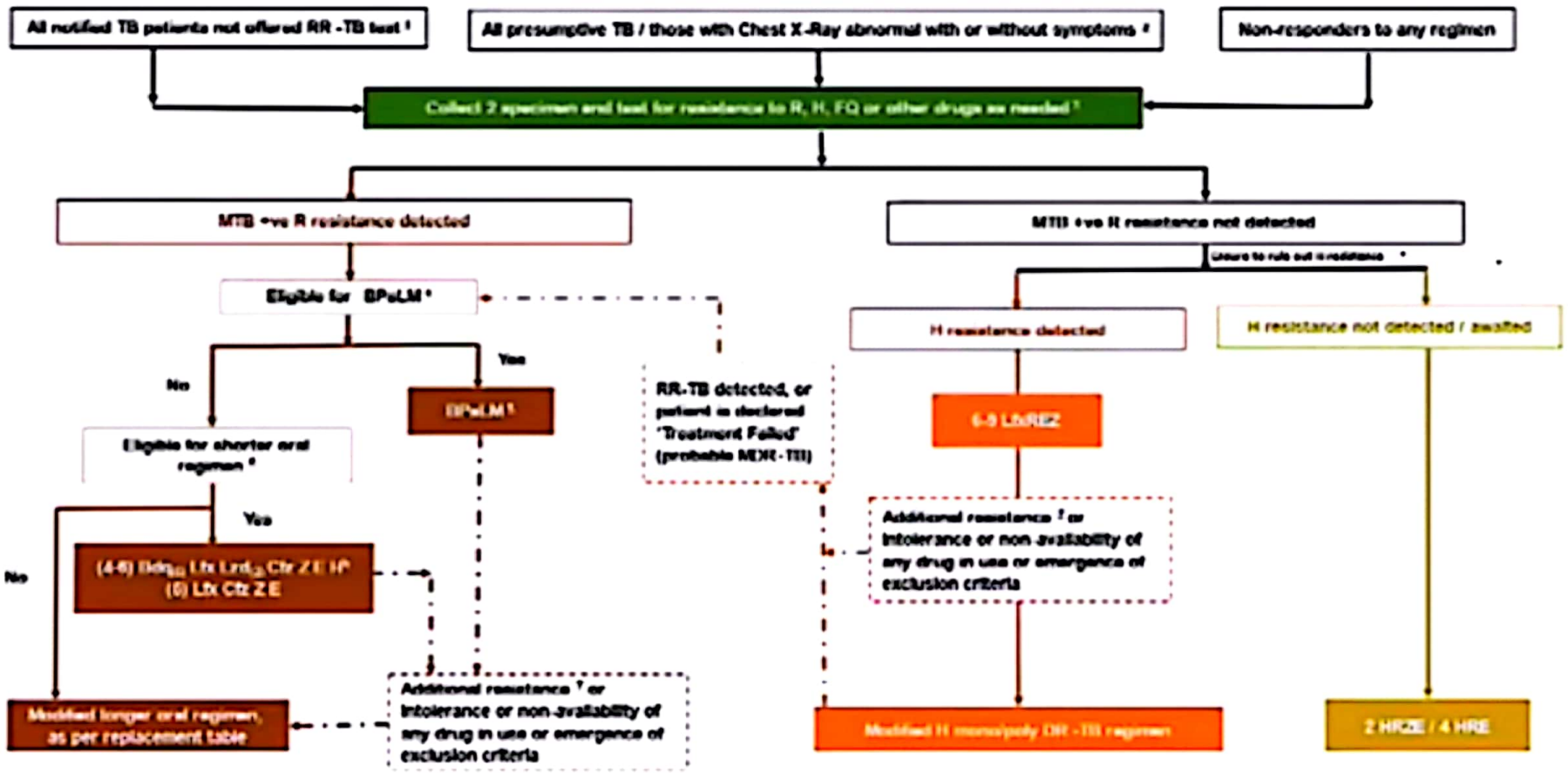
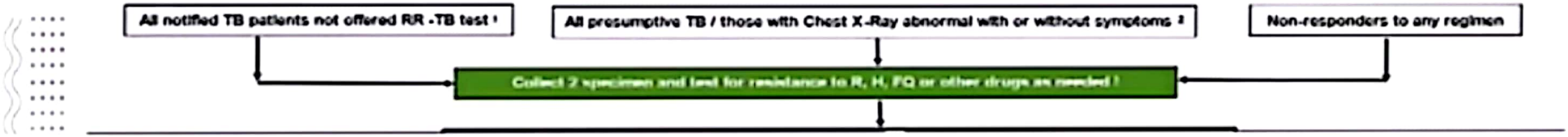
# Integrated Diagnostic and Treatment Algorithm for Drug Susceptible or Resistant Tuberculosis


All notified TB patients not offered RR -TB test
All presumptive TB / those with Chest X-Ray abnormal with or without symptoms
Non-responders to any regimen
MTB +ve R resistance detected
MTB +ve R resistance not detected
Eligible for BPaLM
Yes
No
RR-TB detected, or patient is declared 'Treatment Failed' (probable MDR-TB)
H resistance detected
H resistance not detected / awaited
6-9 LfxREZ
Eligible for shorter oral regimen
Yes
No
(6) Lfx Cfz Z E
Additional resistance or intolerance or non-availability of any drug in use or emergence of exclusion criteria
Additional resistance or intolerance or non-availability of any drug in use or emergence of exclusion criteria
2 HRZE / 4 HRE

Ministry of Health & Family Welfare
Government of India

# Integrated Diagnostic and Treatment


All notified TB patients not offered RR -TB test [1]
All presumptive TB / those with Chest X-Ray abnormal with or without symptoms [2]
Non-responders to any regimen
Collect 2 specimen and test for resistance to R, H, FQ or other drugs as needed [1]



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# Please ensure

1. Includes TB patients diagnosed based on smear microscopy, clinical/ radiological assessment, and histopathology on appropriate specimen
2. Presumptive TB includes those with chest X-ray abnormality with or without symptoms. States to accelerate upfront use of chest X-rays for screening and use of NAAT for TB diagnosis
3. Sputum (two specimens), gastric lavage (GL), induced sputum (IS), broncho-alveolar lavage (BAL), other respiratory specimen and extra pulmonary specimen like fine needle aspiration cytology (FNAC) of peripheral lymph nodes (LNs) and cerebrospinal fluid (CSF), to be sent to NAAT site for M.tb/Rif, followed by

i. NAAT M.tb/XDR (whenever available) for H, FQ, SLI, Eto resistance detection among M.tb detected using the same specimen, wherever the test is available. Until NAAT M.tb/XDR is available for the district, send second specimen for FL-LPA for H resistance detection among M.tb detected followed by SL-LPA for FQ, SLI resistance detection among H or R resistance detected
ii. Baseline culture to be done for all DR-TB specimen received at C&DST lab for baseline liquid culture (LC) DST to Mfx 1.0, Lzd, Z, Bdq*, Pa*, Dlm* (*whenever available)
iii. Start treatment based on NAAT M.tb Rif/ XDR/ LPA and modify based on LC-DST results whenever available
iv. Start treatment based on NAAT M.tb Rif/XDR and modify based on LPA or LC-DST results whenever available

All EP-TB specimens except FNAC of peripheral LNs and CSF preferably to be sent directly to C&DST laboratory for further processing. For processing FNAC and CSF specimen at NAAT sites, refer to the **Guidelines for PMDT in India - 2021**. InhA mutation is associated with Eto resistance. Use other exclusion criteria to decide regimen, if FL-LPA is done on culture isolates for patients with smear negative specimen. Results of Mfx, Am and Eto will be interpreted as per the mutation pattern of rapid molecular test/ LPA.

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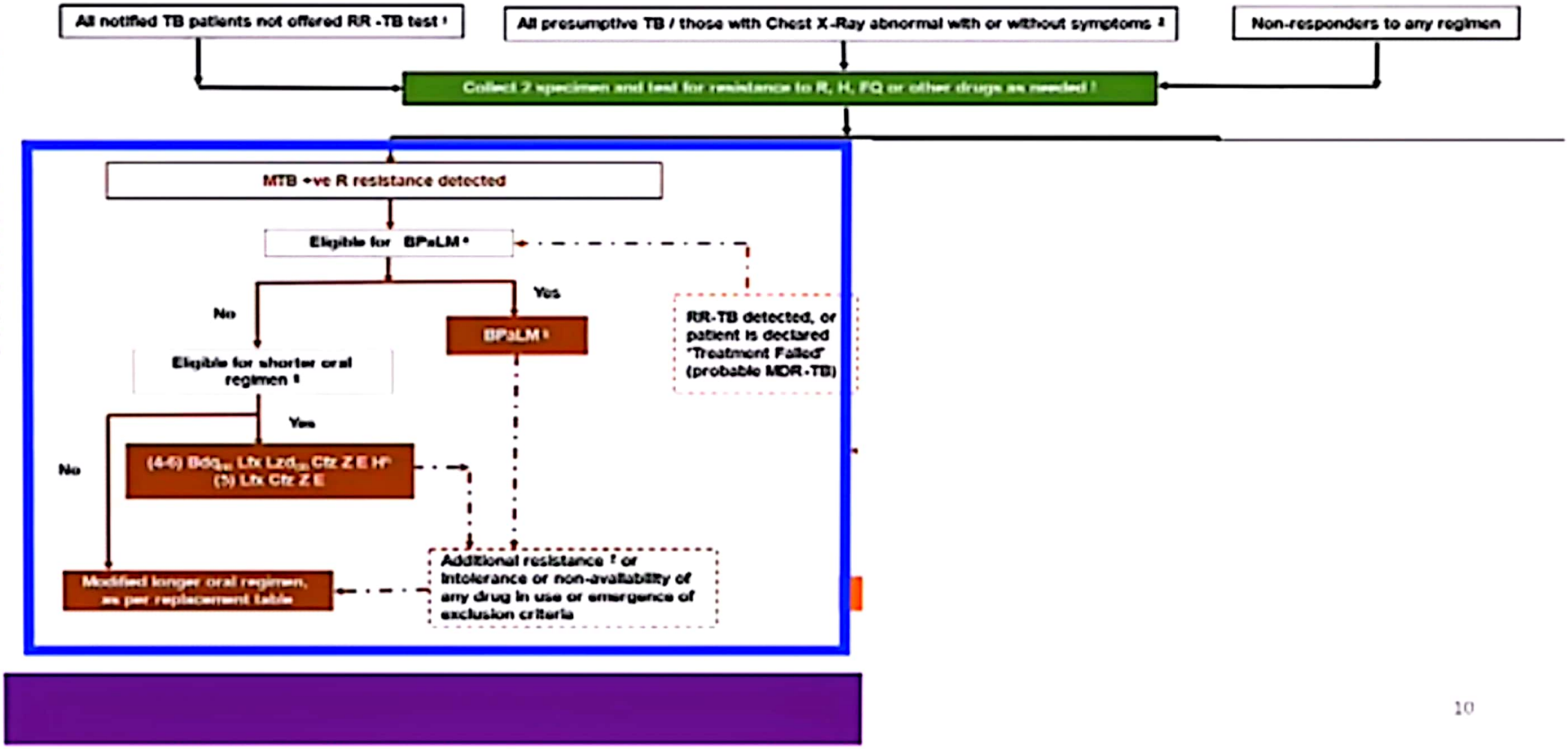
Ministry of Health & Family Welfare
Government of India

# Integrated Diagnostic and Treatment


All notified TB patients not offered RR -TB test ¹
All presumptive TB / those with Chest X-Ray abnormal with or without symptoms ²
Non-responders to any regimen
Collect 2 specimen and test for resistance to R, H, FQ or other drugs as needed ³
MTB +ve R resistance detected
Eligible for BPaLM ⁴
Yes
No
BPaLM ⁵
RR-TB detected, or patient is declared "Treatment Failed" (probable MDR-TB)
Eligible for shorter oral regimen ⁶
Yes
No
(4-6) Bdq 6m Lfx Lzd 6m Cfz Z E H⁷
(3) Lfx Cfz Z E
Additional resistance ⁷ or intolerance or non-availability of any drug in use or emergence of exclusion criteria
Modified longer oral regimen, as per replacement table



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# Treatment regimen for drug-resistant TB

1. 6 months shorter oral - BPaLM
2. 9- month shorter oral MDR/RR-TB regimen
3. Longer oral M/XDR –TB regimen
4. H mono/ poly DR-TB regimen.

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# Pre-treatment evaluation for MDR/RR TB patients

1. Complete Blood Count (Hb, TLC, DLC, Platelet count)
2. RBS
3. B. Urea & S. Creatinine
4. Audiometry (only if on injectable)
5. Liver Function Tests
6. Thyroid Stimulating Hormone levels to assess the thyroid function (TSH levels alone are usually sufficient to assess the thyroid function of the patient)
7. Urine examination – Routine and Microscopic
8. Psychiatric evaluation if required
9. Serum electrolytes (Na, K, Mg, Ca) only for new drugs
10. S. protein (Albumin, Globulin and total proteins) (only if on Dlm)
11. ECG (if on Mfx, Bdq, Cfz or Dlm)
12. urine pregnancy test (in women of reproductive age group)
13. Ophthalmologist opinion – rule out chorioretinitis/uveitis (only if on Linezolid)
14. Surgical evaluation should be done at appropriate time

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# Notes

4 Eligibility criteria for BPaLM:

i. Age 14 years and above

ii. New microbiologically confirmed RR-TB requiring a new course of treatment

iii. Person with exposure of less than one month intake of Bdq, Lzd and/or Pa in the past

or

Person with exposure of more than one month intake of Bdq, Lzd and/or Pa and documented sensitivity to both the drugs.

or

People who had not failed treatment with Bdq or Lzd containing shorter or longer regimen, unless sensitivity to these drugs are documented

i. People with no significant conduction abnormalities in the heart including structural heart disease, syncope, long QT syndrome, AV blocks , Reentry arrhythmias etc apart from asymptomatic QTcF>500ms), not on anti-psychiatric medication

ii. People with no significant liver dysfunction [LFT (Liver enzymes and/ or total bilirubin) <3xUpper Limit of Normal (ULN)]

iii. Non-lactating women, non-pregnant or pregnant women with <24 weeks gestation and who is willing for medical termination of pregnancy (MTP)

iv. People with no severe forms of extrapulmonary-MDR-TB like CNS TB, skeletal TB or disseminated TB

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# Notes

5. Implementation considerations/ Extension criteria for BPaLM: (Details mentioned in Section BPaLM 3.2.1.1c- Regimen modification)
6. Eligibility criteria for shorter oral MDR/RR-TB regimen:
   i. Rifampicin resistance detected/inferred
   ii. MDR/RR-TB with H resistance detected or inferred based on InhA mutation only or based on KatG mutation only (not both)
   iii. MDR/RR-TB with FQ resistance not detected
   iv. No history of exposure to previous treatment with second-line medicines in the regimen (Bdq, Lfx, Cfz or Lzd as applicable) for more than one month (unless susceptibility to these medicines is confirmed)
   v. No extensive TB disease (presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography)
   vi. No severe forms of extra-pulmonary TB or disseminated TB
   vii. Non-pregnant or pregnant women with < 24 weeks gestation and is willing for MTP, if Eto is considered in the regimen
7. If culture/smear remains positive after 4 months of DR-TB treatment, offer LC-DST for Mfx 1.0, Lzd, Z, Bdq*, Pa*, Dlm*. (*whenever available)

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# Current TB Diagnostic landscape

**Dr Bharti Malhotra**

**Sr Professor Microbiology**

**SMS Medical College Jaipur**

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## WHO Endorsed TB Diagnostics

| Technology Class | Products |
|---|---|
| Low complexity automated NAATs for detection of TB and resistance to rifampicin | Xpert® MTB/RIF and Xpert® MTB/RIF Ultra (Cepheid)<br>Truenat™ (Molbio) |
| Low complexity manual NAATs for detection of TB | TB-LAMP (Eiken) |



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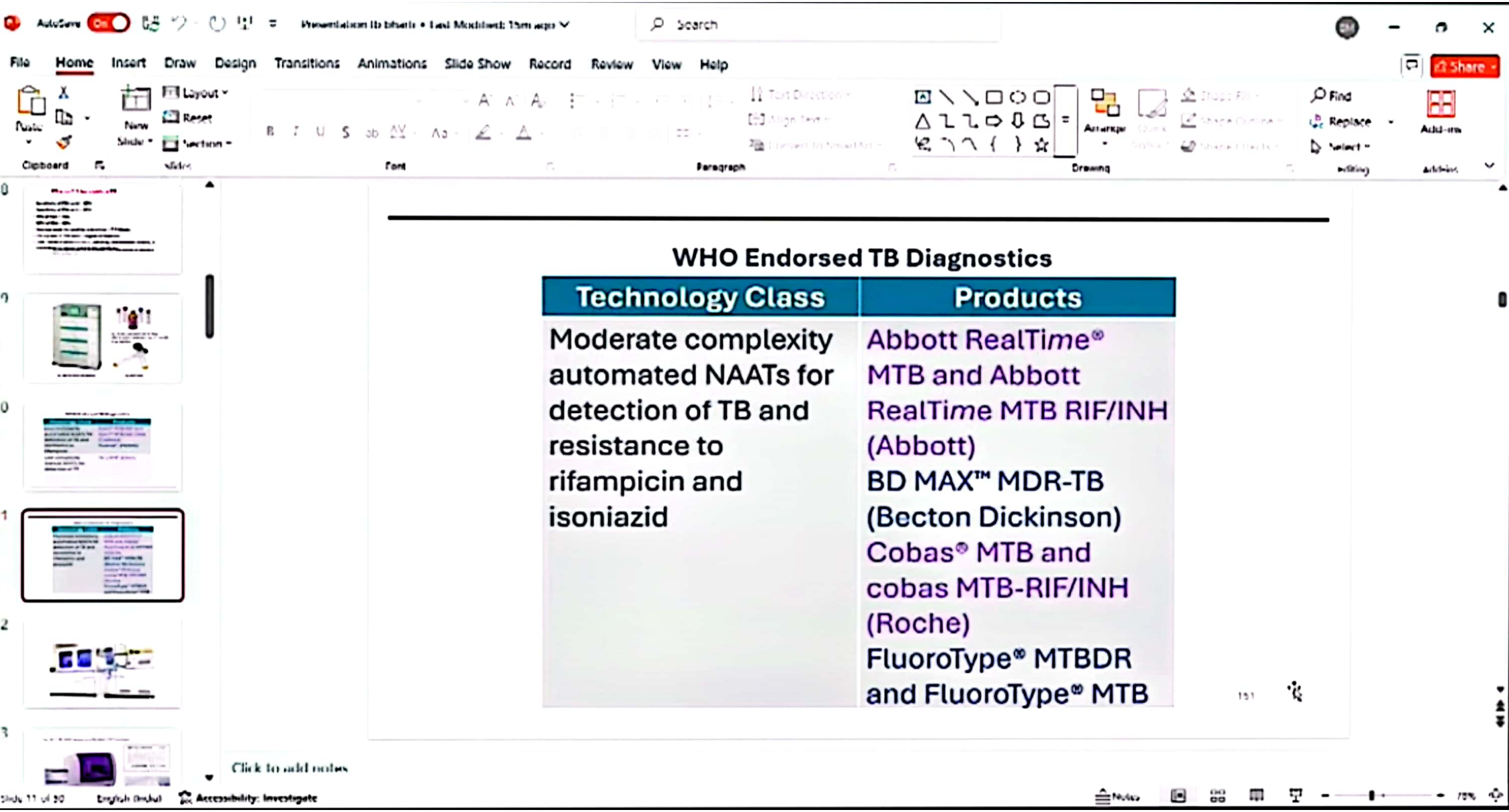
File Home Insert Draw Design Transitions Animations Slide Show Record Review View Help
Share
WHO Endorsed TB Diagnostics
Technology Class
Products
Moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid
Abbott RealTime® MTB and Abbott RealTime MTB RIF/INH (Abbott)
BD MAX™ MDR-TB (Becton Dickinson)
Cobas® MTB and cobas MTB-RIF/INH (Roche)
FluoroType® MTBDR and FluoroType® MTB
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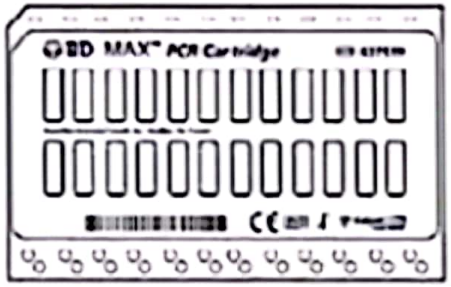
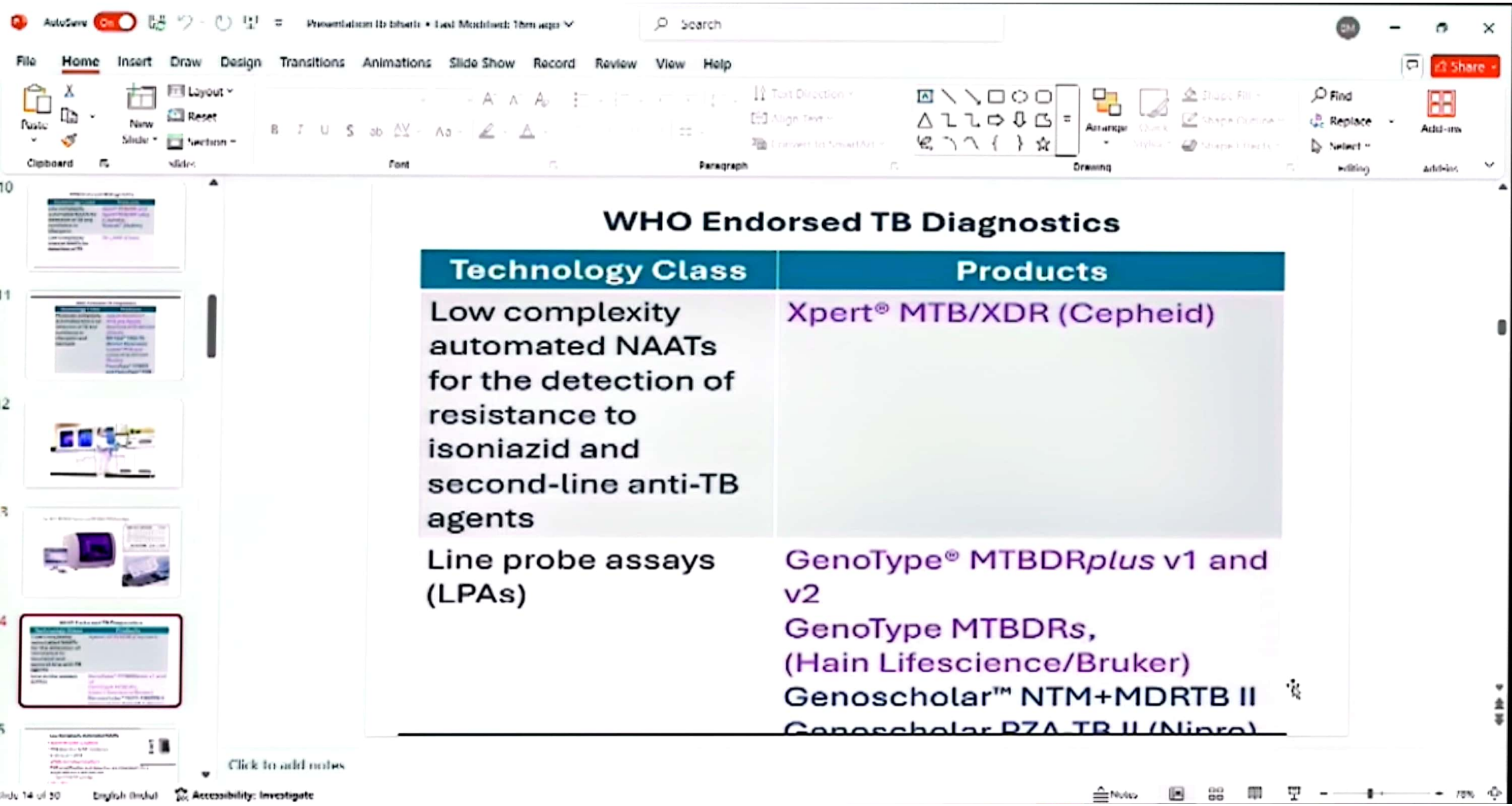
Fig. A2.1. BD MAX System and BD MAX PCR Cartridges




File
Home
Insert
Draw
Design
Transitions
Animations
Slide Show
Record
Review
View
Help
Share
Search
Paste
New Slide
Layout
Reset
Clipboard
Font
Paragraph
Drawing
Find
Replace
Select
Add-ins
WHO Endorsed TB Diagnostics
Technology Class
Products
Low complexity automated NAATs for the detection of resistance to isoniazid and second-line anti-TB agents
Xpert® MTB/XDR (Cepheid)
Line probe assays (LPAs)
GenoType® MTBDRplus v1 and v2
GenoType MTBDRs,
(Hain Lifescience/Bruker)
Genoscholar™ NTM+MDRTB II
Click to add notes
Accessibility: Investigate

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## Low Complexity Automated NAATs

- Xpert® MTB/RIF (Cepheid)
- MTB detection & RIF resistance
- Endorsed in 2010
- qPCR, GeneXpert platform
- PCR amplification and detection are integrated into a single self-enclosed test unit
  - Xpert MTB/RIF cartridge
- TAT < 2hrs
- Target setting: District/ Sub-district lab
- Uninterrupted and stable electrical power supply, temperature control and yearly calibration of the instrument's modules

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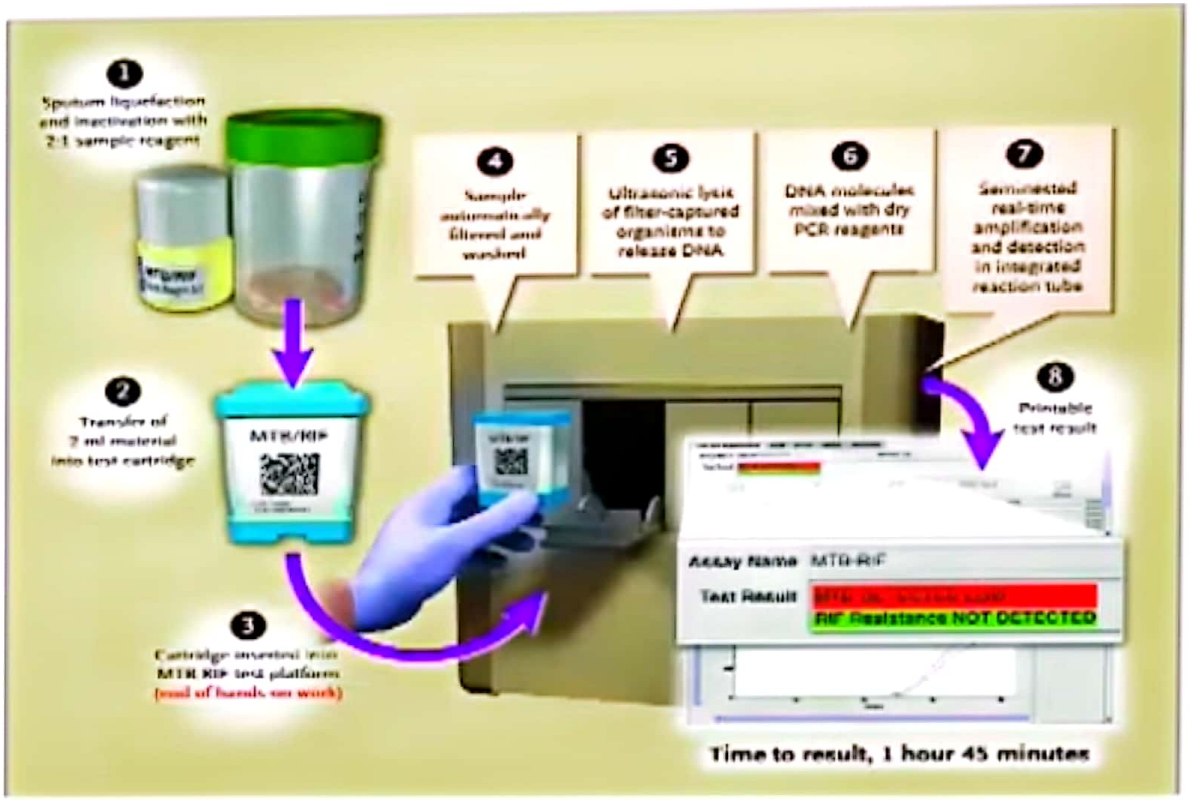


**Fig: Workflow of GeneXpert MTB/RIF assay**

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| Technology | Salient recommendations |
| --- | --- |
| Xpert MTB/RIF | **Adults & children with S/S of pulmonary TB**<br>• Sputum<br>• Children: gastric aspirate, nasopharyngeal aspirate and stool<br>• Initial diagnostic test<br><br>**Adults & children with S/S of TB Meningitis**<br>• CSF<br>• Initial diagnostic test<br><br>**Adults & children with S/S of extrapulmonary TB**<br>• Lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine |

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## Low Complexity Automated NAATs

- Xpert® MTB/RIF Ultra(Cepheid)
- Next generation, endorsed in 2017
- Higher analytical sensitivity
- LoD: 16 cfu/ml vs 114 cfu/ml
- Two different multicopy amplification targets (IS6110 and IS1081)
- Larger DNA reaction chamber: 50µl vs 25µl
- Improve the accuracy of rifampicin-resistance detection
  - Tm analysis

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| Technology | Salient recommendations |
|---|---|
| Xpert MTB/RIF Ultra | **S/S of pulmonary TB**<br>• Adults (without recent H/O TB)<br>• Children<br>• Sputum and nasopharyngeal aspirate<br>• Initial diagnostic test<br><br>**Adults & children with S/S of TB Meningitis**<br>• CSF<br>• Initial diagnostic test<br><br>**Adults & children with S/S of extrapulmonary TB**<br>• Lymph node aspirate, lymph node biopsy |

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## Low Complexity Automated NAATs

- Truenat MTB, MTB Plus and MTB-RIF Dx assays
- Made in India
- qPCR, chip-based
- DNA extraction and amplification separate
- Reflex testing for rifampicin resistance
- TAT < 2hrs
- Battery operated
- Target setting: Peripheral lab
- Multiple pipetting steps

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## Low Complexity Automated NAATs

- Truenat MTB, MTB Plus and MTB-RIF Dx assays
- Made in India
- qPCR, chip-based
- DNA extraction and amplification separate
- Reflex testing for rifampicin resistance
- TAT < 2hrs
- Battery operated
- Target setting: Peripheral lab
- Multiple pipetting steps

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| Technology | Salient recommendations |
| --- | --- |
| Truenat MTB plus<br>Truenat MTB-RIF Dx | • Adults & children with S/S of pulmonary TB<br>• Sputum<br>• Initial diagnostic test |

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## Low Complexity Manual NAATs

- Loopamp Mycobacterium tuberculosis complex (MTBC) detection kit (Eiken Chemical Company, Tokyo, Japan)
- Only MTB detection (without DST)
- LAMP
- Endorsed in 2016
- Manual assay
- TAT < 2hrs
- Target setting: Peripheral lab

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| Technology | Salient recommendations |
| --- | --- |
| Loopamp MTBC | • Adults with S/S of pulmonary TB<br>• Sputum<br>• May be used as replacement of microscopy<br>• Initial smear-negative: follow-on test |

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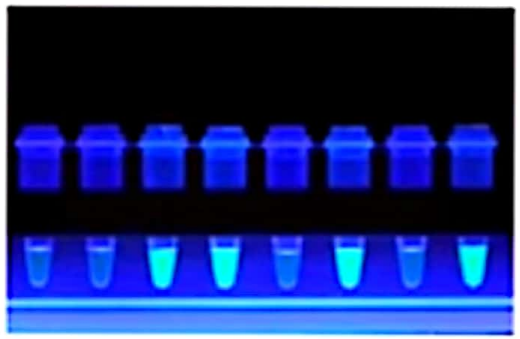

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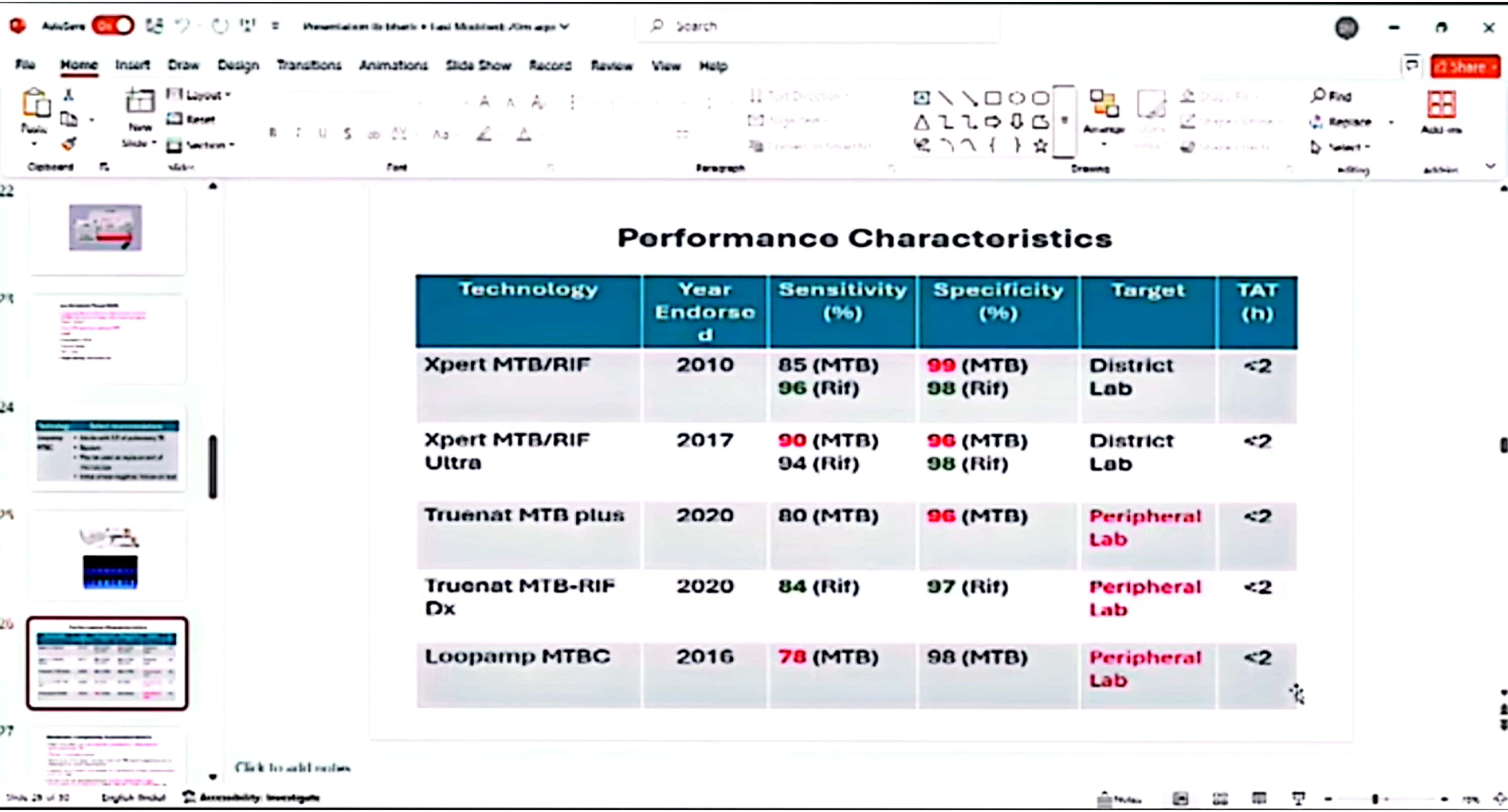
File Home Insert Draw Design Transitions Animations Slide Show Record Review View Help
Share
Performanco Characteristics
Technology | Year Endorsed | Sensitivity (%) | Specificity (%) | Target | TAT (h)
Xpert MTB/RIF | 2010 | 85 (MTB) 96 (Rif) | 99 (MTB) 98 (Rif) | District Lab | <2
Xpert MTB/RIF Ultra | 2017 | 90 (MTB) 94 (Rif) | 96 (MTB) 98 (Rif) | District Lab | <2
Truenat MTB plus | 2020 | 80 (MTB) | 96 (MTB) | Peripheral Lab | <2
Truenat MTB-RIF Dx | 2020 | 84 (Rif) | 97 (Rif) | Peripheral Lab | <2
Loopamp MTBC | 2016 | 78 (MTB) | 98 (MTB) | Peripheral Lab | <2
Click to add notes

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## Moderate Complexity Automated NAATs

- High burden of isoniazid-resistant, rifampicin-susceptible TB
- Often undiagnosed
- Address this gap: detection of TB and resistance to rifampicin and isoniazid
- Faster and less complex to perform than phenotypic DST & LPA
- Most run on established multi-disease high throughput platforms (HIV, HCV): high volume of testing required
- Automated/ manual DNA extraction, rest automated
- Target setting: Reference laboratory
- Rapid sample referral system required

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| Technology | Salient recommendations |
| --- | --- |
| Moderate complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid | • People with signs and symptoms of pulmonary TB<br>• Respiratory samples<br>• May be used |

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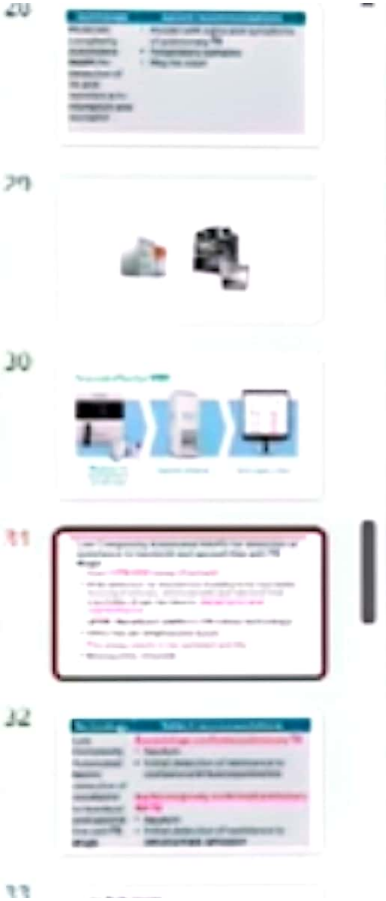

## Low Complexity Automated NAATs for detection of resistance to isoniazid and second-line anti-TB drugs

- Xpert MTB/XDR assay (Cepheid)
- MTB detection & resistance mutations to isoniazid, fluoroquinolones, ethionamide and second-line injectable drugs (amikacin, kanamycin and capreomycin)
- qPCR, GeneXpert platform (10-colour technology)
- WHO has de-emphasized SLIDs
- The assay needs to be updated quickly
- Bedaquiline, linezolid

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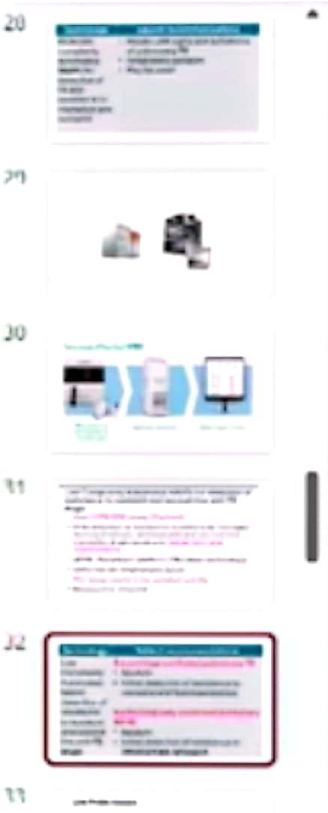

| Technology | Salient recommendations |
|---|---|
| Low Complexity Automated NAATs detection of resistance to isoniazid and second-line anti-TB drugs | **Bacteriology confirmed pulmonary TB**<br>• Sputum<br>• Initial detection of resistance to isoniazid and fluoroquinolones<br><br>**Bacteriologically confirmed pulmonary RR-TB**<br>• Sputum<br>• Initial detection of resistance to ethionamide, amikacin |

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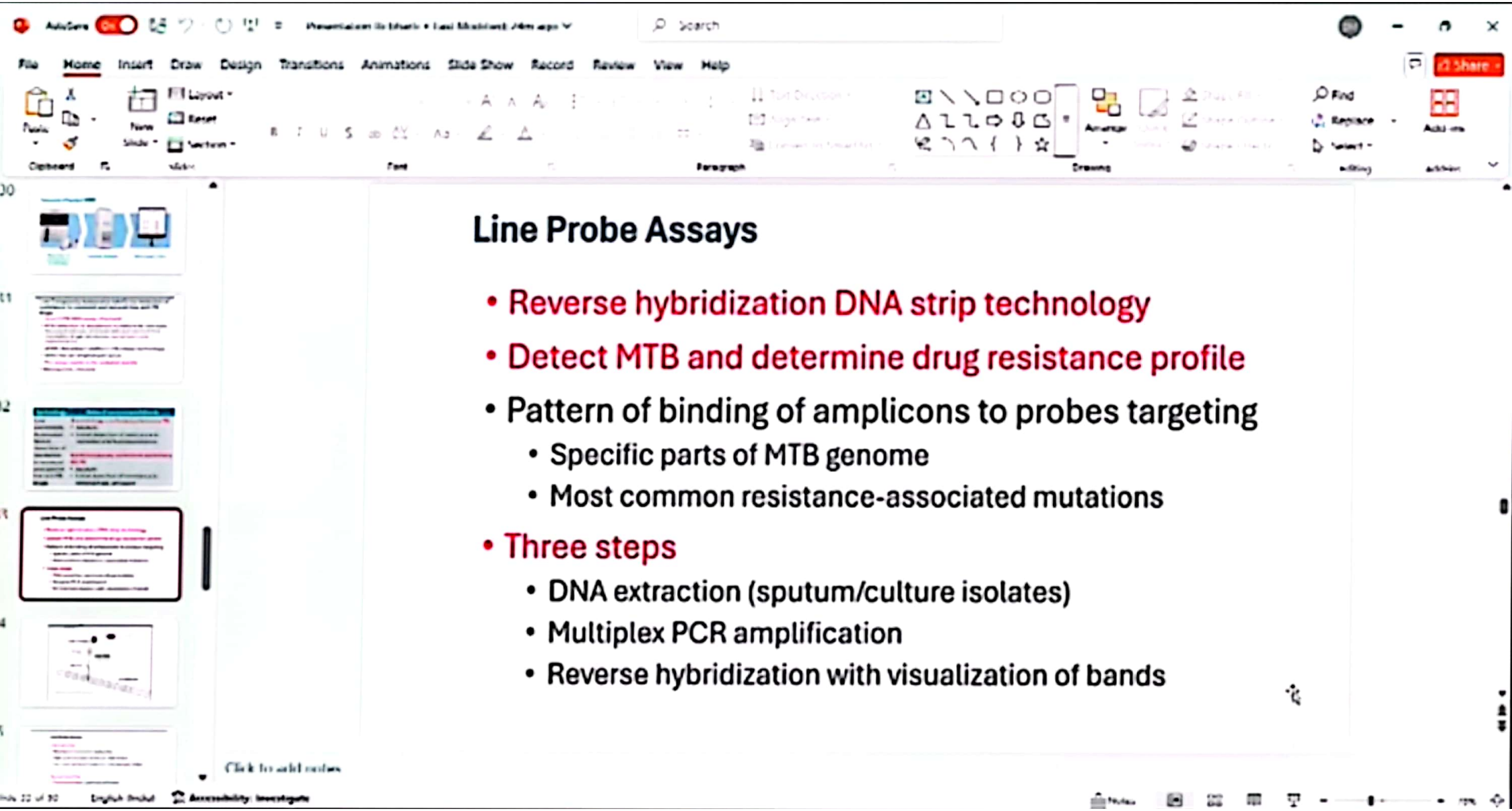
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Review
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Line Probe Assays
• Reverse hybridization DNA strip technology
• Detect MTB and determine drug resistance profile
• Pattern of binding of amplicons to probes targeting
• Specific parts of MTB genome
• Most common resistance-associated mutations
• Three steps
• DNA extraction (sputum/culture isolates)
• Multiplex PCR amplification
• Reverse hybridization with visualization of bands

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## Line Probe Assays

### First line-LPAs

- Rifampicin resistance: *rpoB* probes
- High-level isoniazid resistance: *katG* probes
- Low-level isoniazid resistance: *inhA* promoter probes

### Second line-LPAs

- Fluoroquinolones: *gyrA* and *gyrB probes*
- SLIDs: *rrs* and *eis* promoter probes

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| Technology | Salient recommendations |
| --- | --- |
| First-line LPA | • Sputum-smear positive or culture isolate<br>• Detect resistance to rifampicin and isoniazid<br>• May be used as an initial test |
| Second-line LPA | • Confirmed MDR/RR-TB<br>• Sputum-smear positive or culture isolate<br>• Detect resistance to fluoroquinolones and SLIDs<br>• May be used as an initial test |

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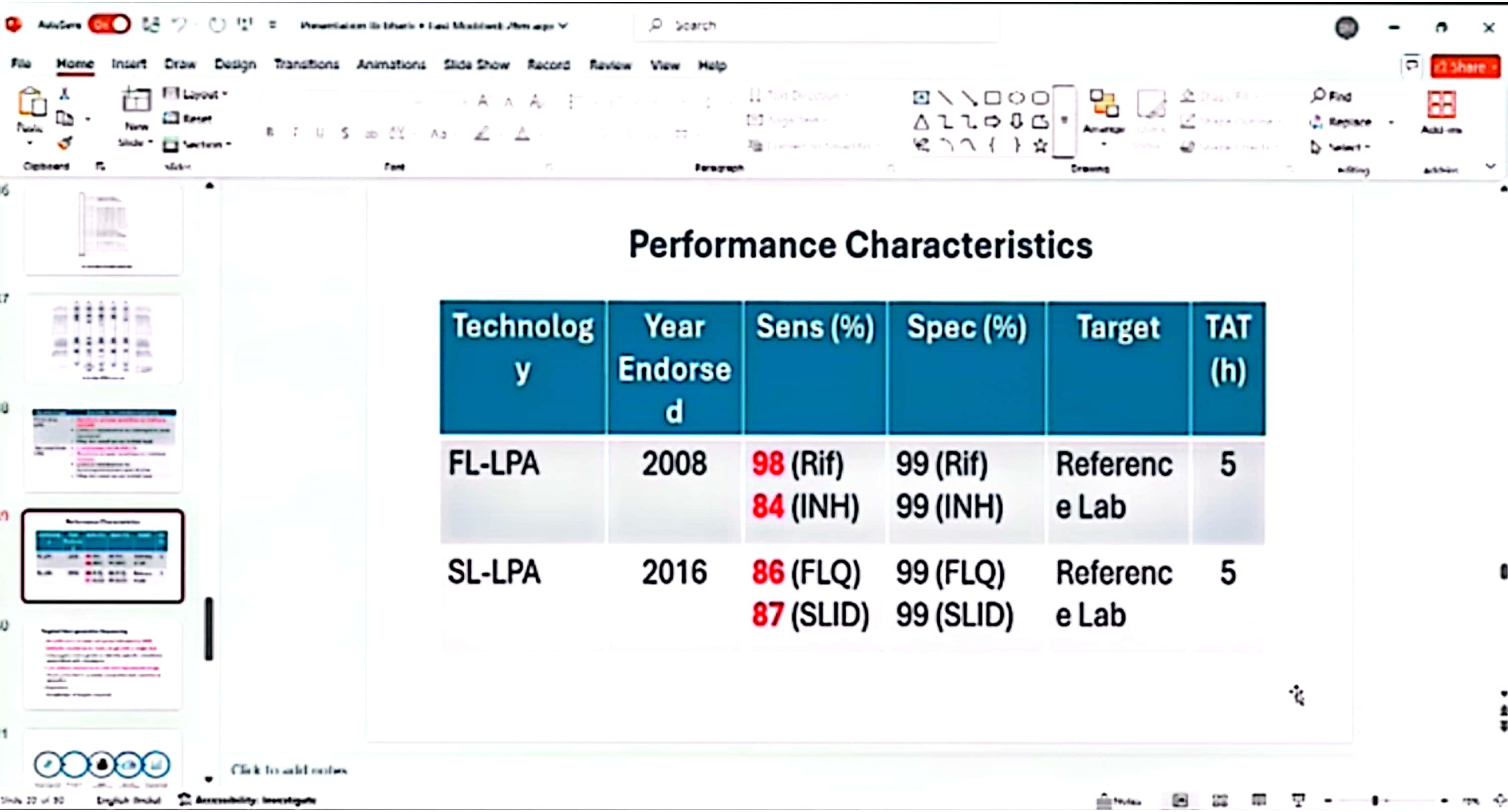
File Home Insert Draw Design Transitions Animations Slide Show Record Review View Help
Share
Performance Characteristics
Technology
Year Endorsed
Sens (%)
Spec (%)
Target
TAT (h)
FL-LPA
2008
98 (Rif)
84 (INH)
99 (Rif)
99 (INH)
Reference Lab
5
SL-LPA
2016
86 (FLQ)
87 (SLID)
99 (FLQ)
99 (SLID)
Reference Lab
5
Click to add notes

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## Targeted Next-generation Sequencing

- Amplification of selected genes followed by NGS
- Detects resistance to many drugs with a single test
- Interrogate entire genes to identify specific mutations associated with resistance
- Can detect resistance to new and repurposed drugs
- Great potential to provide comprehensive resistance detection
- Expensive
- Knowledge of targets required

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DEEPLEX® MYC-TB KIT

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| Technology | Salient recommendations |
| --- | --- |
| Targeted NGS | • Bacteriologically confirmed pulmonary TB disease<br>• Respiratory samples<br>• Rifampicin, isoniazid, pyrazinamide and ethambutol<br>• Fluoroquinolones, bedaquiline, linezolid, clofazimine, amikacin and streptomycin |

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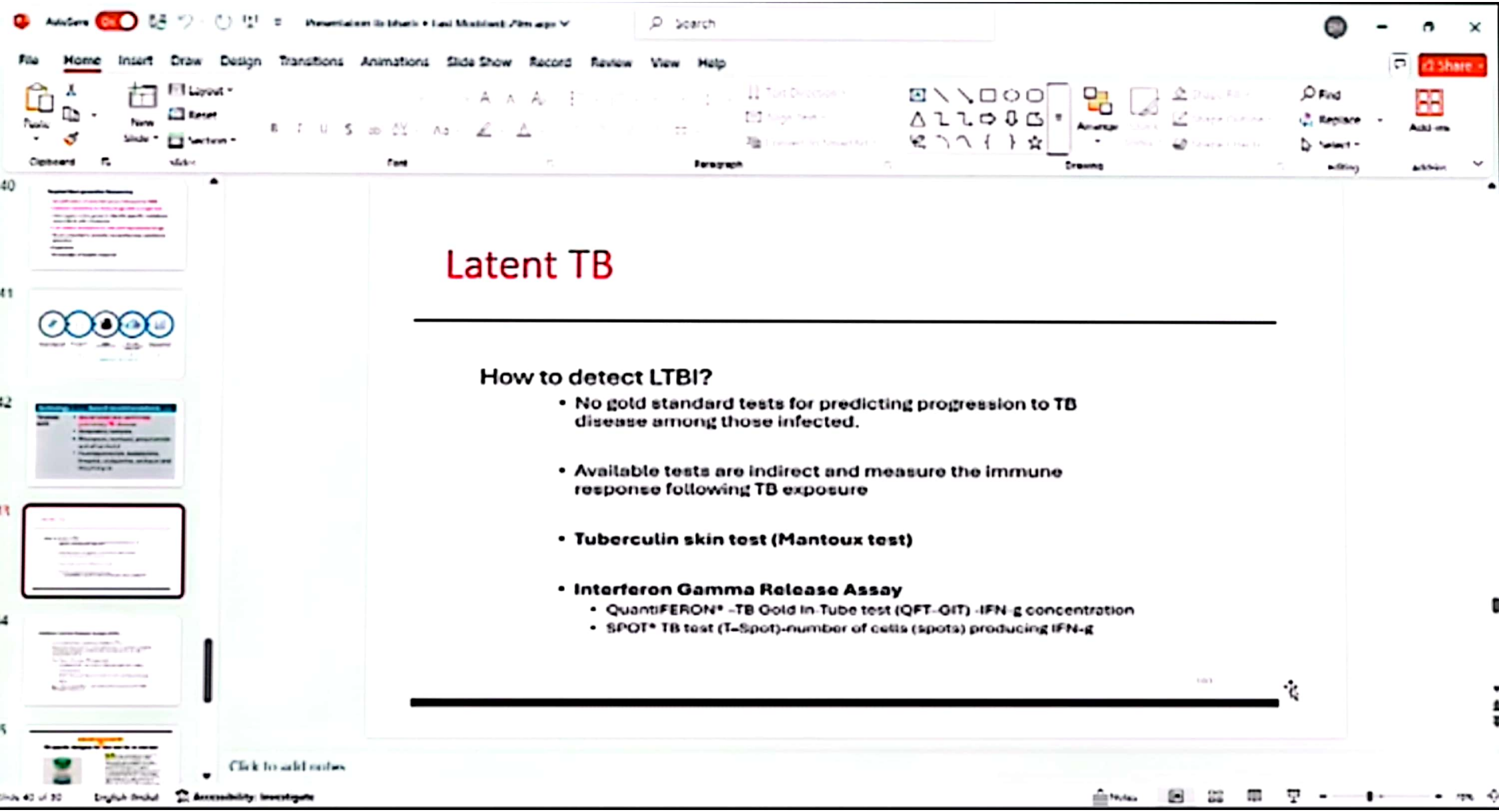
File Home Insert Draw Design Transitions Animations Slide Show Record Review View Help
Latent TB
How to detect LTBI?
No gold standard tests for predicting progression to TB disease among those infected.
Available tests are indirect and measure the immune response following TB exposure
Tuberculin skin test (Mantoux test)
Interferon Gamma Release Assay
QuantiFERON® -TB Gold In-Tube test (QFT-GIT) -IFN-g concentration
SPOT® TB test (T-Spot)-number of cells (spots) producing IFN-g

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## Interferon Gamma Release Assays (IGRA)

- In-vitro blood test- measures release of IFN-γ
- Measures responses to a well defined mix of synthetic peptides simulating antigenic proteins that are specific for TB- TB 7.7, ESAT-6 and CFP-10
- Two Types of Assays (FDA approved)
  - QuantiFERON® –TB Gold In-Tube test (QFT–GIT) -IFN-g concentration
  - SPOT® TB test (T–Spot)-number of cells (spots) producing IFN-g
- Quantiferon Gold Plus – new test which measures both CD4+ and CD8+ responses

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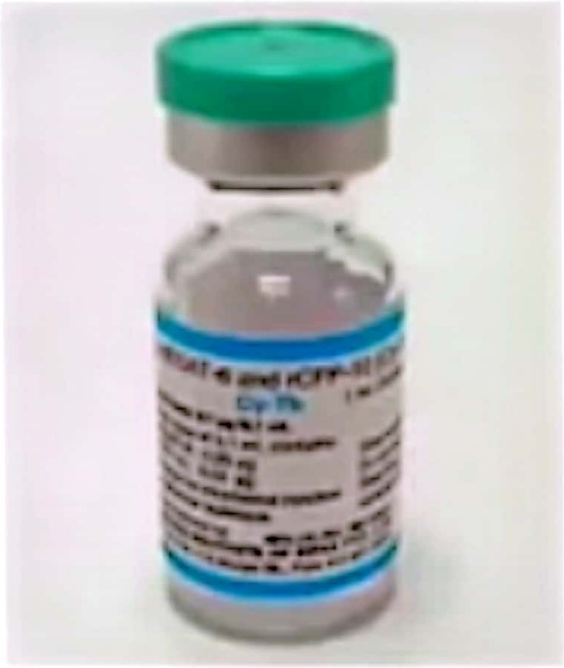
Is the child infected with TB ?

TBI

# TB specific Antigens for skin test for *in vivo* test



- **Cy-Tb** was manufactured by the Statens Serum Institut (SSI), Denmark, as a solution of two recombinant proteins of ESAT-6 and CFP-10 (in a 1:1 ratio), produced by genetically modified Lactobacillus lactis. One single test dose of 0.1 mL contains 0.05 µg of rd ESAT-6 and 0.05 µg of rCFP-10. In 2019, SSI entered into a partnership with the Serum Institute of India, which is licensed to produce and distribute the test.

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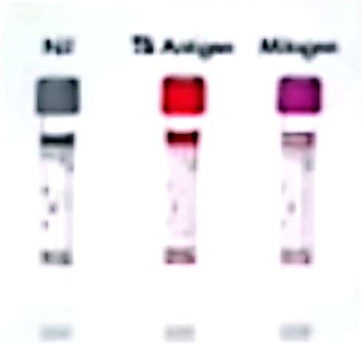
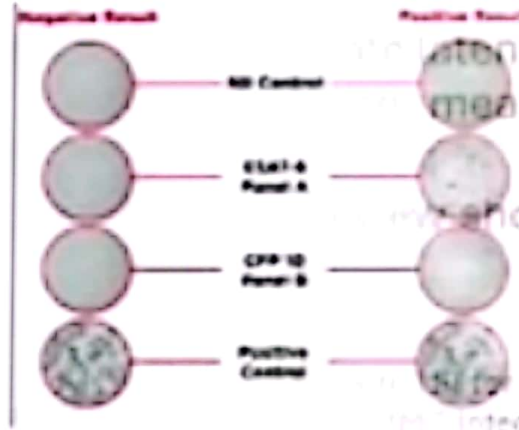
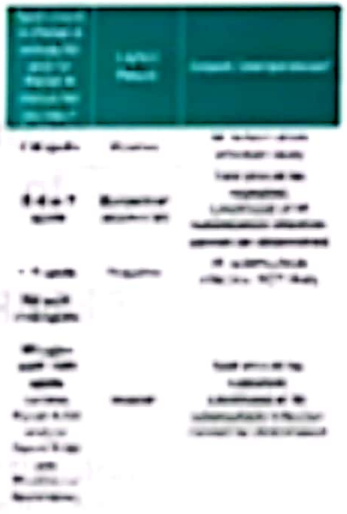
# IGRA- Quantiferon TB Gold





- Test interpretation



# Comparison between TST and IGRA test

| | TST | IGRA |
|---|---|---|
| Specificity | Low in BCG vaccinated | High also in BCG vaccinated |
| Sensitivity | High | High |
| Ease of use | Field friendly, complex test interpretation | Require labs and infrastructure |
| Cost of test | Low | High |
| Manufacturing | Complex old product | Complex, multiple components |
| **Special populations** | | |
| Children | Affected by young age | Affected by young age |
| PLHIV | Requires info on HIV status for correct interpretation | Affected by HIV and low CD4 count |

- ✓ Neither test can separate latent infection from active TB disease
- ✓ Screening tests rely on measurements of adaptive host immune responses to bacteria
- ✓ A recent systematic review showed no significant difference between both the tests for LTBI

Auguste P, et al. Comparing IGRA with TST for identifying LTBI that progresses to active TB: systematic review & meta-analysis. BMC Infect Dis. 2017 Mar 9;17(1):200.

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# Whom to test for LTBI

- In children >5 years and adults HHC with pulmonary* TB patients, TST or IGRA testing would be offered wherever available.
- In other risk groups, TST or IGRA are to be performed for considering TPT after ruling out active TB, especially if the prevalence of TB among these risk groups is low.

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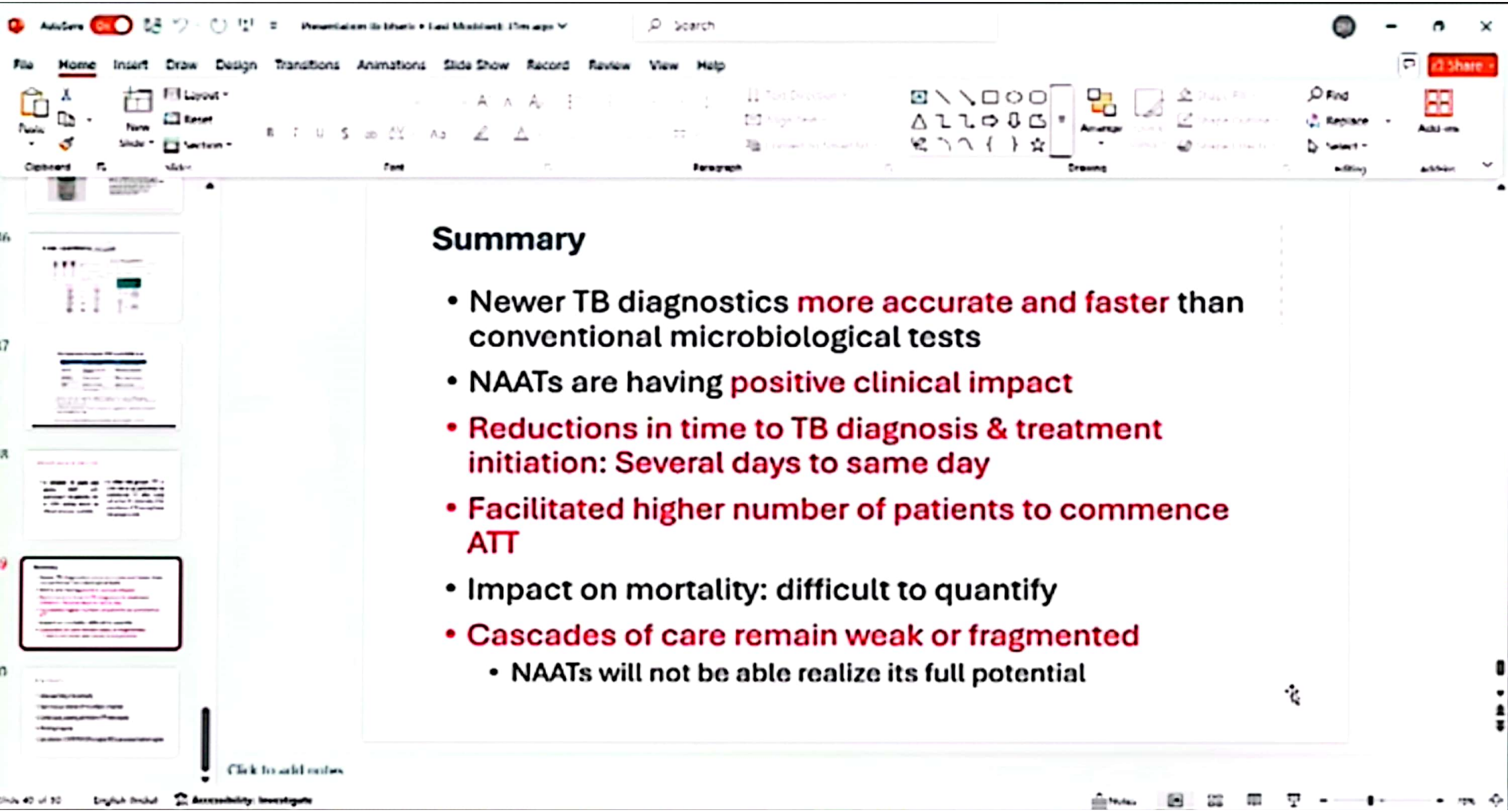
Summary
• Newer TB diagnostics more accurate and faster than conventional microbiological tests
• NAATs are having positive clinical impact
• Reductions in time to TB diagnosis & treatment initiation: Several days to same day
• Facilitated higher number of patients to commence ATT
• Impact on mortality: difficult to quantify
• Cascades of care remain weak or fragmented
• NAATs will not be able realize its full potential

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icmr | NIRT
INDIAN COUNCIL OF MEDICAL RESEARCH
NATIONAL INSTITUTE FOR RESEARCH IN TUBERCULOSIS

# BPaLM Regimen and Role of BDQ DST

Dr S Siva Kumar, Scientist E and Head
Department of Bacteriology
ICMR-National Institute for Research In Tuberculosis
Chennai

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# Trials

- NIX TB trial
  - 92% favourable outcome at 6months post treatment with BPaL (1200mg) in DRTB
  - Peripheral neuropathy – 81%, Anemia – 37%
  - WHO recommendation of BPaL 1200mg for MDRTB (2020)

- ZeNix TB trial
  - 93% and 89 % with BPaL 1200mg and 600mg for 26 weeks at the end of 78 wks of post treatment follow up
  - Peripheral neuropathy 38% and 24% wth LZD 1200mg and 600mg

- BEAT study experience (Bdq, DLM, LZD (600mg), CFZ)
  - Peripheral neuropathy -42%
  - Anemia 47%
  - LZD Dose reduction to 300mg in 45 patients, cured -40

Conradie et al. N Engl J Med 2020;382:893-902. Conradie et al. N Engl J Med 2022;387:810-823.

Padmapriyadarsini et al. 2022 Jun 29;76(3):e938-e946.

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# BPaLM regimen

The all oral BPaLM regimen consists of:

- **Bedaquiline (BDQ)** – Bedaquiline is a diarylquinoline antimycobacterial that Targets TB bacteria by inhibiting ATP synthase.

- **Pretomanid (Pa)** – A nitroimidazole drug that disrupts TB bacterial cell walls by inhibiting synthesis of mycolic acid.

- **Linezolid (L)** – Linezolid is a synthetic oxazolidinone that inhibits bacterial protein synthesis but can have dose-dependent toxicities.

- **Moxifloxacin (M)** – A fluoroquinolone that enhances bactericidal activity by inhibiting DNA gyrase and prevents bacterial cell DNA and RNA synthesis.

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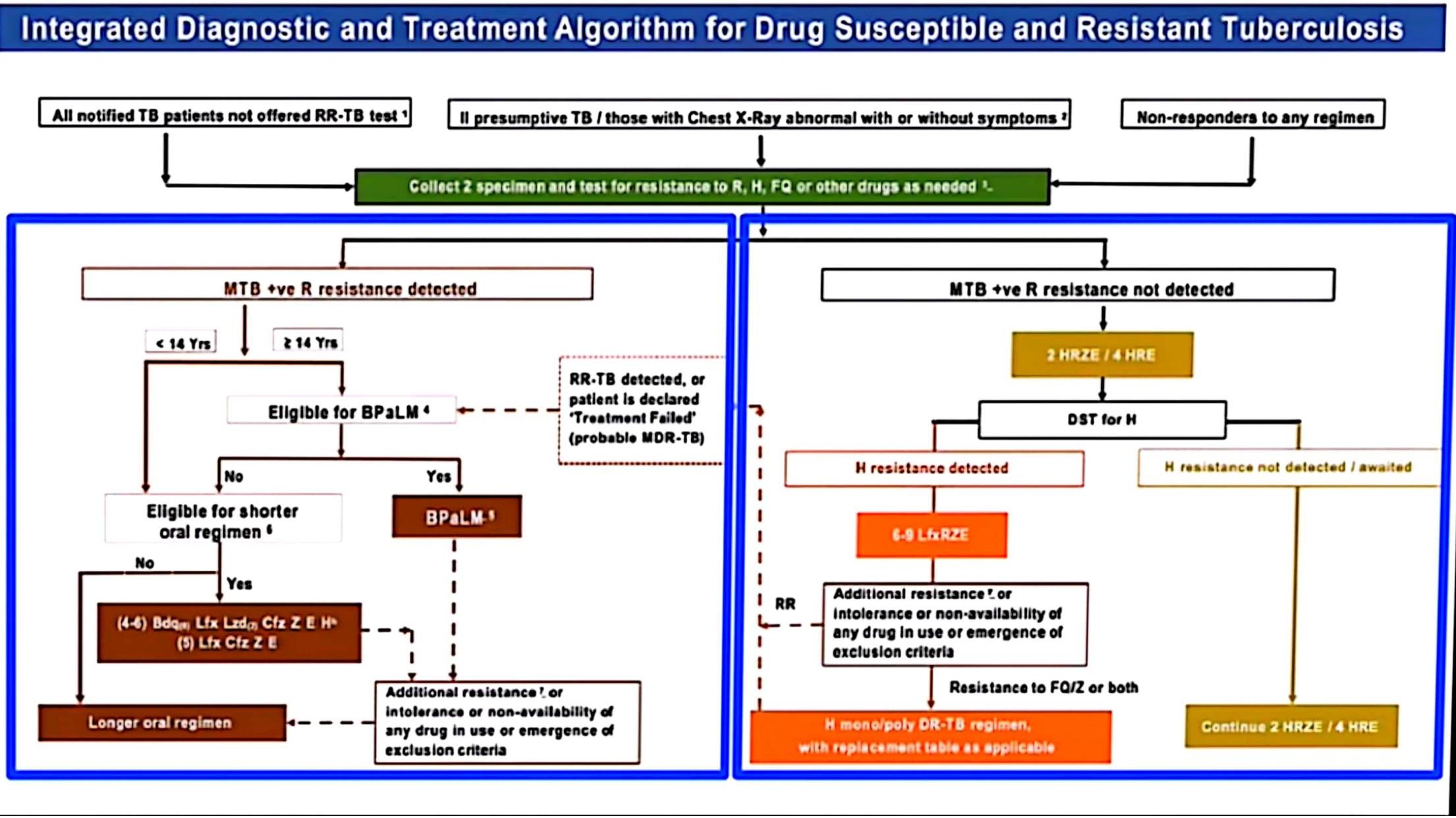
# Integrated Diagnostic and Treatment Algorithm for Drug Susceptible and Resistant Tuberculosis


All notified TB patients not offered RR-TB test [1]
Il presumptive TB / those with Chest X-Ray abnormal with or without symptoms [2]
Non-responders to any regimen
Collect 2 specimen and test for resistance to R, H, FQ or other drugs as needed [3]
MTB +ve R resistance detected
< 14 Yrs
≥ 14 Yrs
Eligible for BPaLM [4]
RR-TB detected, or patient is declared 'Treatment Failed' (probable MDR-TB)
No
Yes
Eligible for shorter oral regimen [6]
BPaLM [5]
No
Yes
(4-6) Bdq(6) Lfx Lzd(2) Cfz Z E H
(5) Lfx Cfz Z E
Additional resistance [7] or intolerance or non-availability of any drug in use or emergence of exclusion criteria
Longer oral regimen
MTB +ve R resistance not detected
2 HRZE / 4 HRE
DST for H
H resistance detected
H resistance not detected / awaited
6-9 LfxRZE
RR
Additional resistance [7] or intolerance or non-availability of any drug in use or emergence of exclusion criteria
Resistance to FQ/Z or both
H mono/poly DR-TB regimen, with replacement table as applicable
Continue 2 HRZE / 4 HRE

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- Administered orally with food and adequate water intake. All patients above 14 years of age receive these doses. There are no weight bands.
- Dosage are given below in table-

| | | | |
|---|---|---|---|
| **Bedaquiline** | First Two Weeks | 400 mg once daily | (4 × Bdq 100 mg tablets) |
| | Weeks 3rd-26/29* | 200 mg three times a week | (2 × Bdq 100 mg tablets) |
| **Pretomanid** | Weeks one to 26-39* | 200 mg daily | (1 × Pa 200 mg tablet) |
| **Linezolid** | Weeks one to 26-39* | 600 mg once daily | (1 x 600 mg tablet) |
| **Moxifloxacin** | Weeks one to 26-39* | 400 mg once daily | (1 x 400 mg tablet) |

*Extension criteria will detailed in implementation considretation and treatment session

- Pyridoxine (Pdx) will be administered for the entire duration of treatment as per weight band
- Temporary cessation – re-introduction could be considered within 30 days after re-assessment by N/DDR-TBC.
- Dose modification, treatment extension, follow up monitoring etc will be discussed in subsequent sessions.

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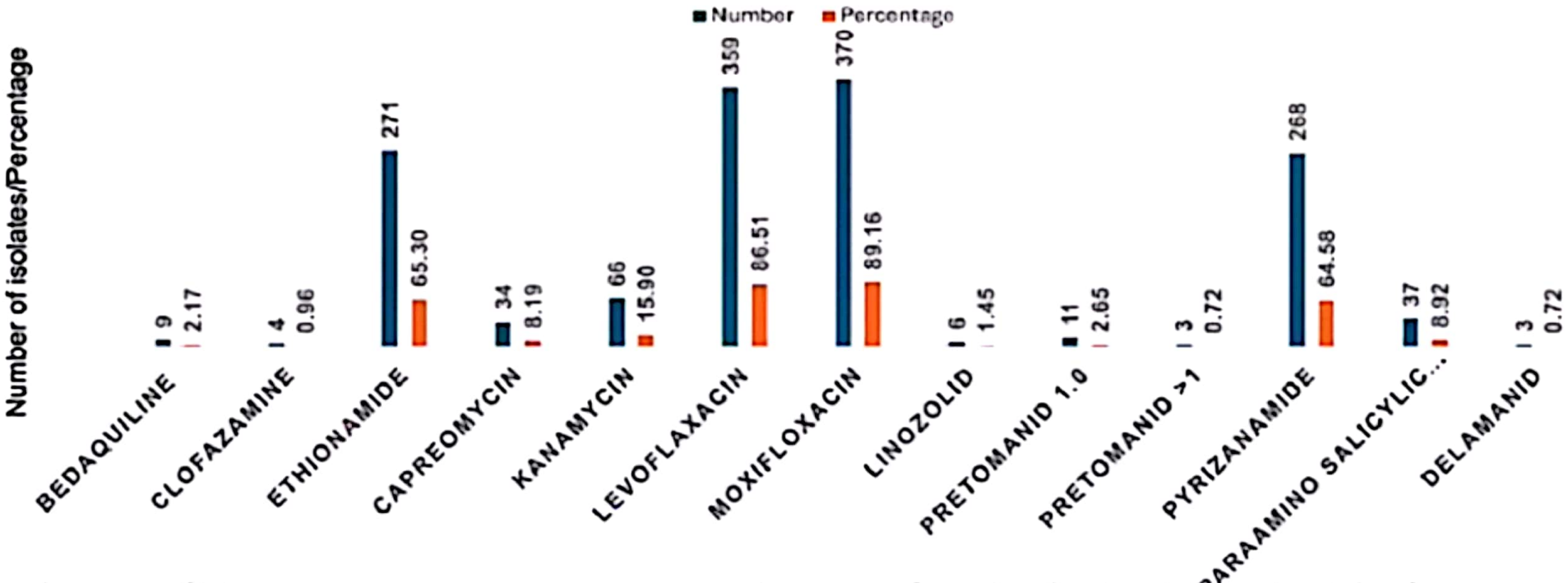
# Studies on BDQ Resistance




The rate of BDQ resistance among MDR-TB isolates was found to be 1.64% (4/243). The frequency of BDQ resistance was higher in patients with the medical history of BDQ treatment (7.14%; 1/14) as compared to naïve cases (1.35%, 3/221). (Dr Ajay vir etal)

Of 117 BDQ-exposed patients from December 2020-December 2022, 42 (36%) exhibited a BDQ-resistant strain (Dr Singla eetal 2025)

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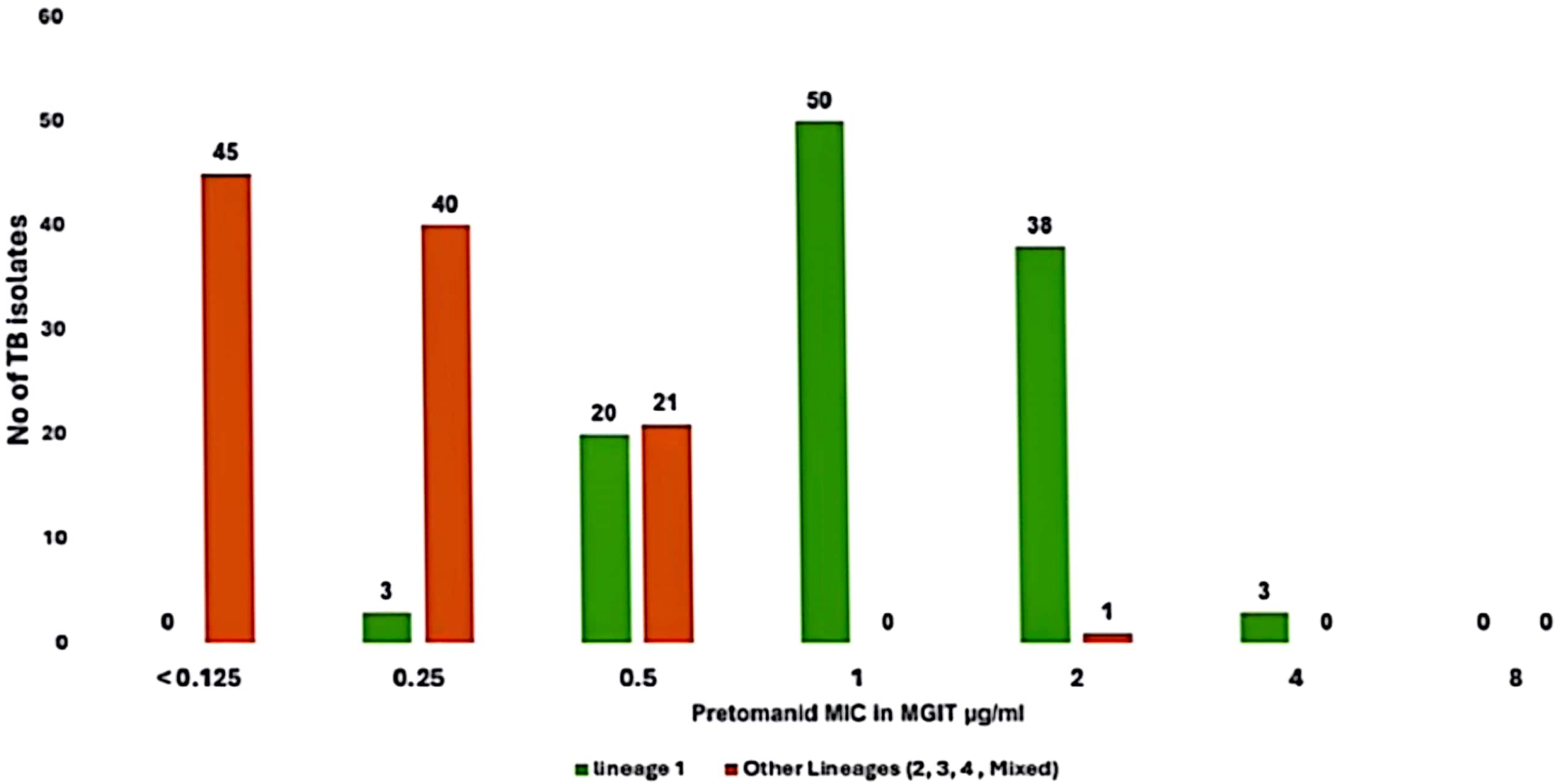
Pretomanid MIC distribution
No of TB isolates
60
50
40
30
20
10
0
45
40
3
20
21
50
0
38
1
3
0
0
0
<0.125
0.25
0.5
1
2
4
8
Pretomanid MIC in MGIT µg/ml
lineage 1
Other Lineages (2, 3, 4 , Mixed)

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# Challenges with Bedaquiline DST

**Challenges with Bedaquiline DST.**

•**Availability**: Bedaquiline DST is not always readily available in all settings, particularly in resource-limited regions where MDR-TB is most prevalent. Limited access to these tests can impact timely and effective treatment decisions.

•**Turnaround Time:** Phenotypic DST methods, particularly broth microdilution, can take several weeks to complete, delaying the initiation of appropriate treatment. Genotypic methods can be faster but require specialized equipment and expertise.

•**Mutation Variability:** While mutations in the **atpE gene** are the most common cause of bedaquiline resistance, new or less understood resistance mechanisms may arise, complicating the interpretation of DST results. In India its Rv0678

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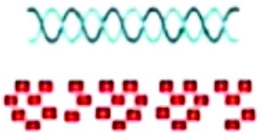
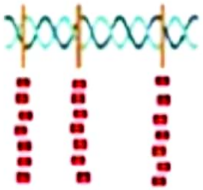
# Targeted NGS enables Rapid & Comprehensive TB DST

Phenotypic DST (pDST)



Whole-genome sequencing (WGS)



Targeted sequencing (tNGS)

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# WGS and TB

- WGS is generally performed only on strains grown in culture.
- Relatively high quantity of good quality DNA to generate full WGS data for a given sample.
- Attempts to perform WGS directly from sputum, results have been variable.

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# Targeted Next Generation sequencing (tNGS)

**Sputum or other clinical sample**

**DNA Extraction**

**Target amplification 28 target**

- Sputum or Culture
- 15 anti-TB Drugs
- Lineage
- Spoligotyping
- Mixed Infection
- Hetero-resistance
- NTM infection

**Sequencing using a portable sequencer**

**Data Analysis**

Sputum → Library preparation → Sequencing → Analysis → Drug resistance Pattern

24 to 48 Hrs

Sputum → *M.tb* Isolate → Library preparation → Sequencing → Analysis → Drug resistance Pattern

10 days to 40 days

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# TB mutational Catalogue

- **Standardized analysis and interpretation of genetic data for resistance prediction → Catalogue of resistance-associated mutations in TB**

- **Version 1 published in 2021**
+ **Data from 38,000 isolates, 40 countries**
+ **Version 2 published in Nov 2023**
+ **Data from additional 15,000 isolates**
+ **increase in geographical and drug coverage**
+ **mutations associated with resistance to new and repurposed drugs (BDQ, CLF, DLM)**

- **Version 1 published in 2022**
+ **Data from 2112 isolates, 28 states**
+ **Version 2 published in 2024**
+ **Data from additional 6782 isolates**
+ **increase in geographical and drug coverage**
+ **mutations associated with resistance to new and repurposed drugs.**

https://www.who.int/publications/i/item/9789240028173



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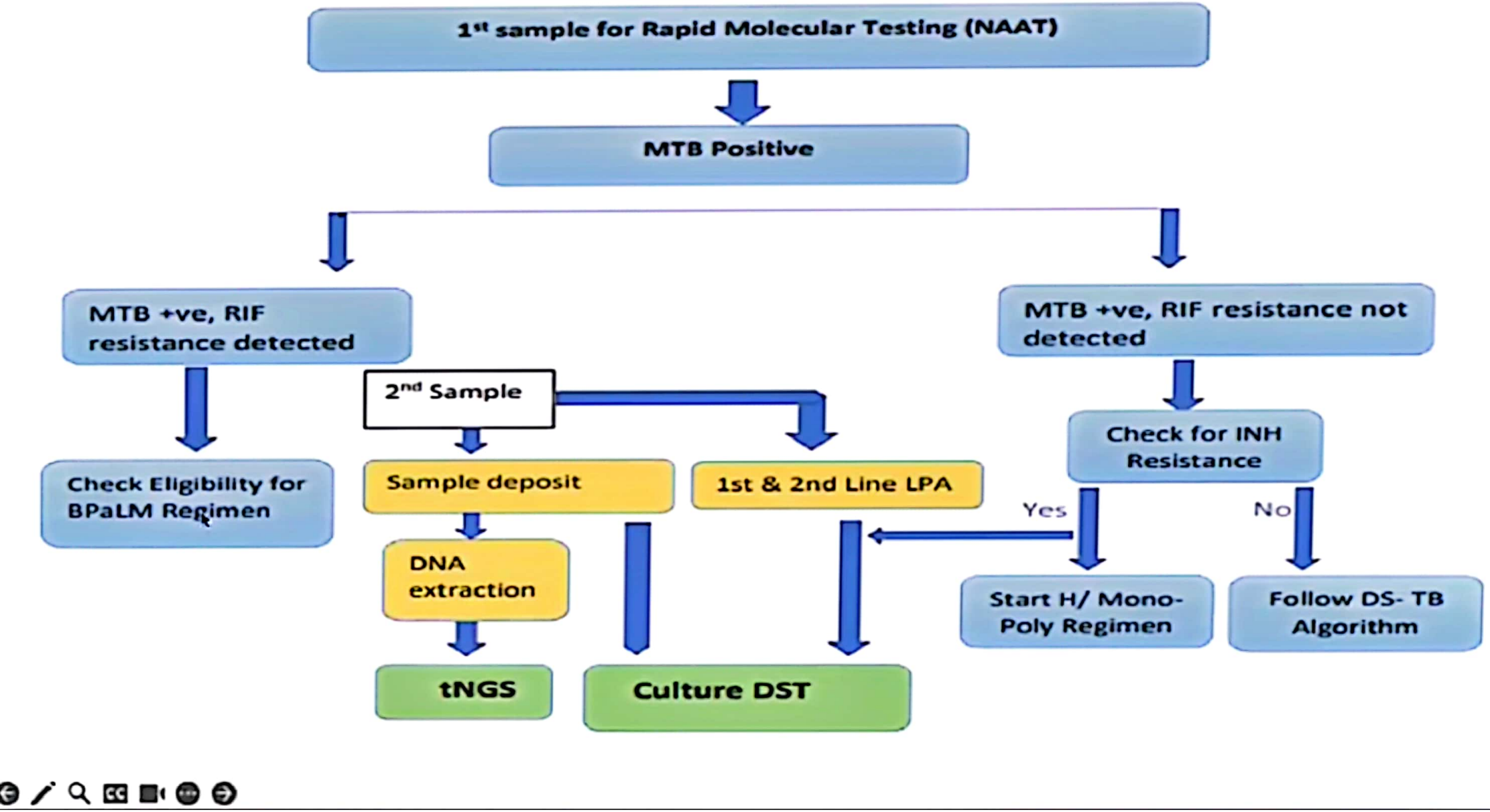
1st sample for Rapid Molecular Testing (NAAT)
MTB Positive
MTB +ve, RIF resistance detected
MTB +ve, RIF resistance not detected
2nd Sample
Check Eligibility for BPaLM Regimen
Sample deposit
1st & 2nd Line LPA
Check for INH Resistance
Yes
No
DNA extraction
Start H/ Mono-Poly Regimen
Follow DS- TB Algorithm
tNGS
Culture DST

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# DR. KOMAL SHAH

**DNB PULMONOLOGY (GOLD MEDALLIST)**
Jaslok Hospital and research centre – Mumbai 2013
**FELLOWSHIP IN INFECTIOUS DISEASES**
CMC Vellore, 2022
**JOHNS HOPKINS INTENSIVE INFECTIOUS DISEASES**
June 2024

**ASSOCIATE PROFESSOR,**
Department of Pulmonology,
Dr. Vasantrao Pawar medical college, Hospital and Research centre,
**CONSULTANT INFECTIOUS DISEASES SPECIALLIST**
Ashoka medicover hospital, NAMCO hospital
Nashik

**NATIONAL FACULTY FOR VARIOUS NATIONAL INTERNATIONAL CONFERENCES**
**BEST PAPER AWARD – NAPCON 2021**
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**BEST PAPER AWARD – MAHACRITICON 2023**
**MUHS RESEARCH AWARD – MARCH 2024**
**ICS ERS TRAVEL GRANT – VIENNA, AUSTRIA - 2024**

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# Types of Drug Resistance Tuberculosis -DRTB

H5Content

There are currently five categories of drug-resistant TB under the National TB Elimination Programme (NTEP):

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# Types of Drug Resistance Tuberculosis -DRTB

**H5Content**

| Types of Drug Resistance TB (DR TB) | Resistance to Isoniazid (H) | Resistance to Rifampicin (R) | Resistance to Fluroquinolone (FQ) •Ofloxacin, •Levofloxacin •Moxifloxacin | Resistance to Group A Drugs •Bedaquiline or •Linezolid |
|---|---|---|---|---|
| **H Mono / Poly Drug Resistance** •**Resistant** to Isoniazid (H) •**Sensitive** to Rifampicin (R) •**Unknown / Sensitive** to Fluoroquinolone (FQ) or Group A Drugs - Bedaquiline or Linezolid | Resistant | Sensitive | Unknown/ Sensitive | Unknown/ Sensitive |
| **Rifampicin Resistance (RR)** •**Resistant** to Rifampicin (R) •**Unknown / Sensitive** to other drugs | Unknown/ Sensitive | Resistant | Unknown/ Sensitive | Unknown/ Sensitive |
| **Multi Drug Resistance TB (MDR TB)** •**Resistant** to Isoniazid (H) and Rifampicin (R) •**Unknown / Sensitive** to Fluoroquinolone (FQ) or Group A Drugs - Bedaquiline or Linezolid | Resistant | Resistant | Unknown/ Sensitive | Unknown/ Sensitive |
| **Pre-Extensive Drug Resistance (Pre -XDR)** •**Resistant** to Isoniazid (H), Rifampicin (R) and any Fluroquinolone (FQ) •**Sensitive/ Unknown** to Group A Drugs - Bedaquiline or Linezolid | Resistant | Resistant | Resistant | Unknown/ Sensitive |
| **Extensive Drug Resistance (XDR)** •**Resistant** to Isoniazid (H) , Rifampicin (R) and any Fluoroquinolone (FQ) and at least one additional Group A Drugs - (presently to either Bedaquiline or linezolid [or both]) | Resistant | Resistant | Resistant | Resistant |

Resistant

Sensitive

Unknown/ Sensitive

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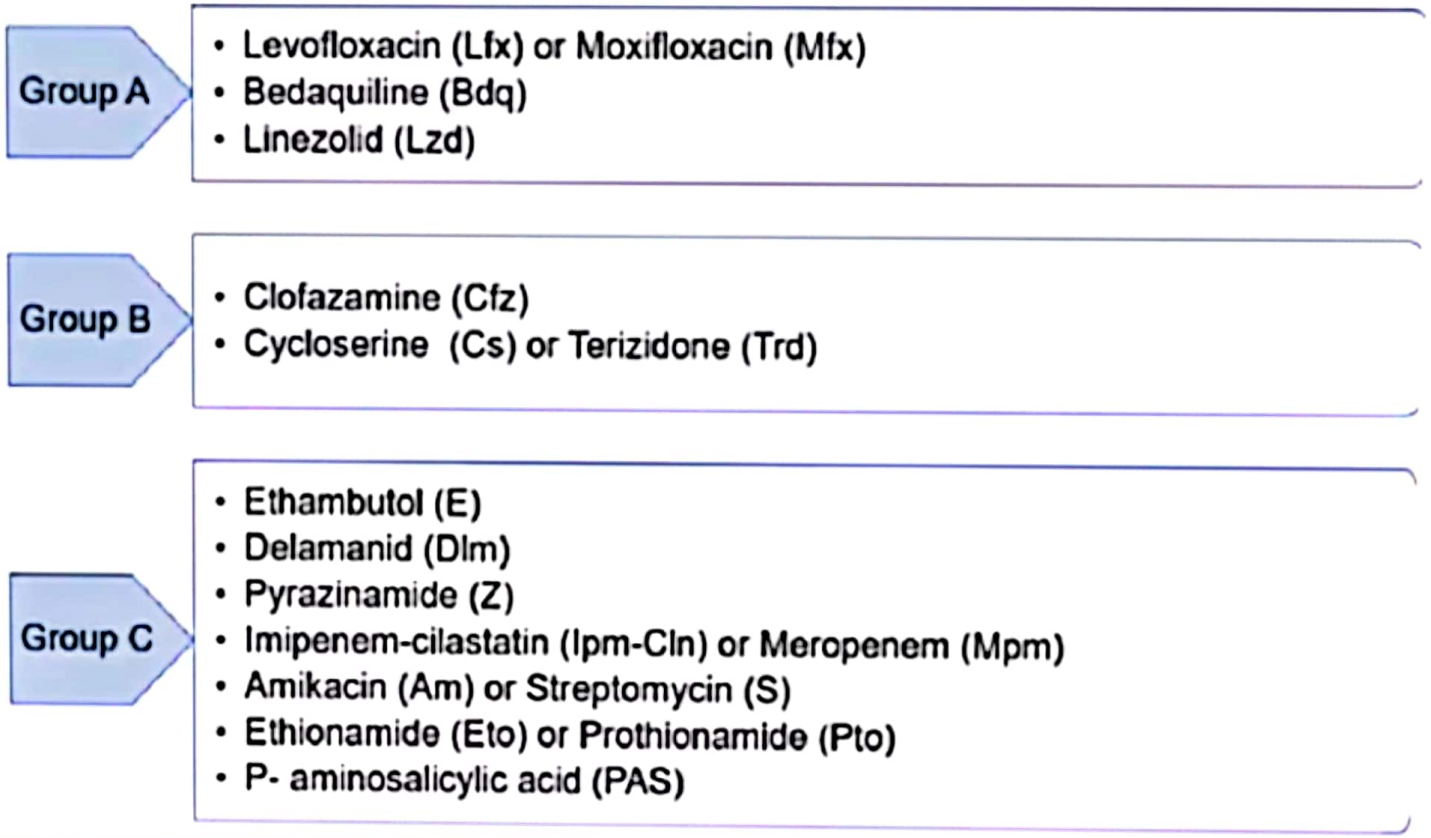
# Second Line anti TB drugs

H5Content

**The anti-TB drugs recommended for treatment of Multi- and Extensively Drug-resistant (M/XDR) TB patients are grouped into three groups – A, B and C (Figure below).**

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Treatment regimen options for DR-TB:

- 6-9 months **BPaLM** shorter oral regimen
- 9-11 months **shorter oral** MDR/RR-TB regimen
- 18-20 months **longer oral** M/XDR –TB regimen
- 6-9 months **H mono/ poly** DR-TB regimen.

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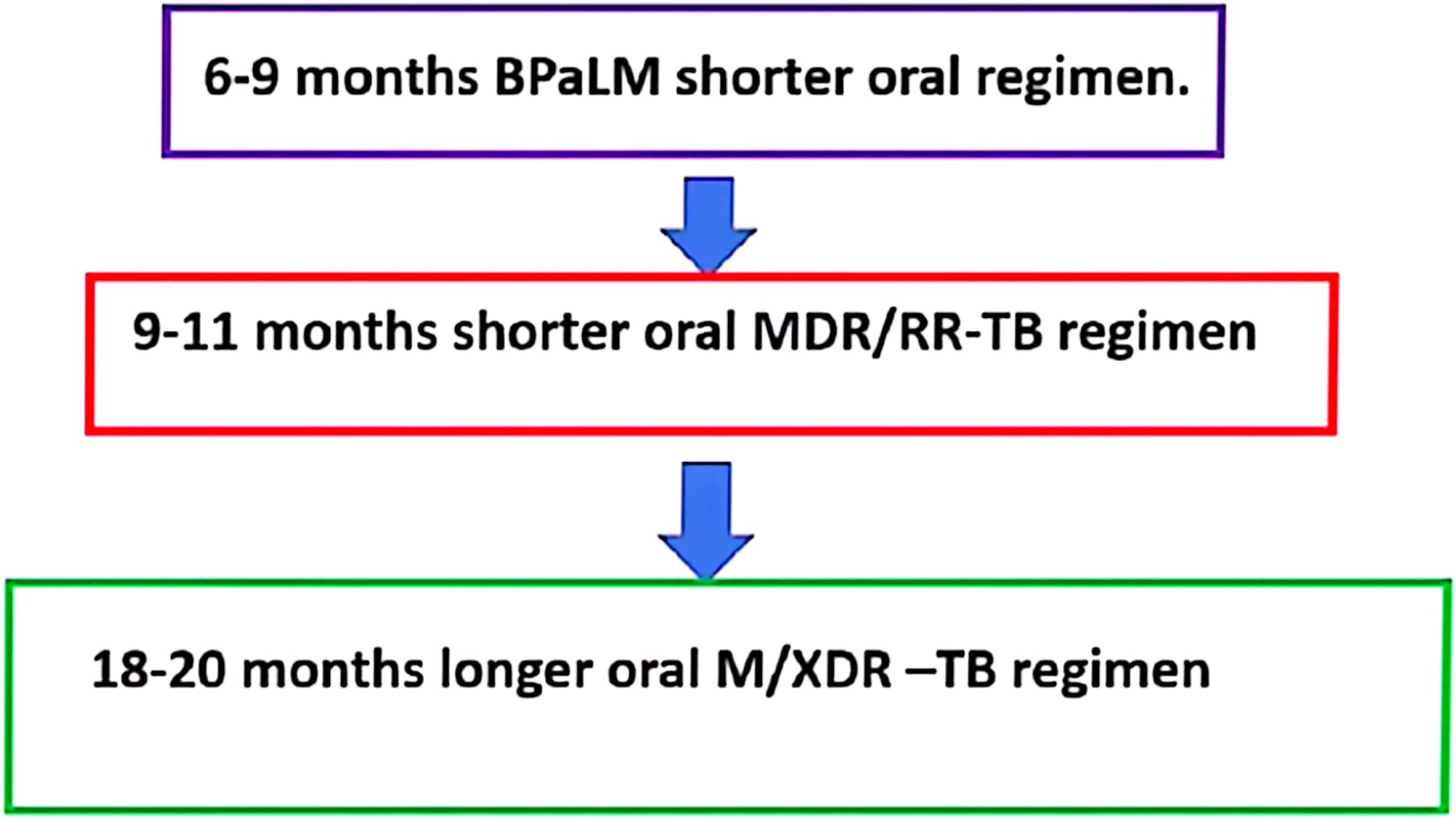
Preference of order

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# BPaLM/ BPaL

- **Bedaquiline is a diarylquinoline**
  - inhibits mycobacterial ATP synthase.

- **Pretomanid(Pa), a nitroimidazooxazine**
  - Inhibits mycolic acid biosynthesis, blocks mycobacterial cell-wall production,
  - Acts as a respiratory poison against nonreplicating bacteria after nitric oxide release under anaerobic conditions.
  - Pa has been approved to use only with the BPaLM/BPaL.

- **Linezolid,**
  - an oxazolidinone that disrupts protein synthesis

- **Moxifloxacin,**
  - inhibit DNA synthesis

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One day of typical BPaL regimen
6 months / <750 pills
One day of typical XDR-TB treatment
18+ months / 14,000+ pills

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## INCLUSION CRITERIA

**1. 14 years** & above with **new microbiologically confirmed MDR/ RRTB** requiring a new course of treatment or probable MDR-TB who failed H mono/ poly DR-TB treatment.

2. H/o of Drug Exposure: of **less than one month** intake of Bdq, Lzd and/ or Pa in the past

or

Exposure of more than one month intake of Bdq, Lzd and/ or Pa and **documented sensitivity** to these drugs

or

Not failed treatment with Bdq or Lzd containing shorter or longer regimen, and sensitivity to these drugs are documented.

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## EXCLUSION CRITERIA

1.< 14 years age

2.Documented resistance to Bdq, Lzd and/ or Pa.

3.LFT (Liver enzymes and/ or total bilirubin) >3xUpper Limit of Normal

4.Severe forms of extrapulmonary-MDR-TB like CNS TB, spinal/ skeletal TB or disseminated TB

5.Cardiac conduction abnormalities - structural heart disease, syncope, long QT syndrome, AV blocks, Reentry arrhythmias

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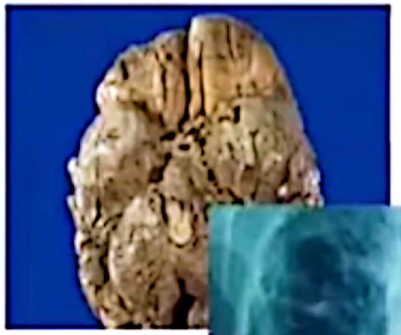

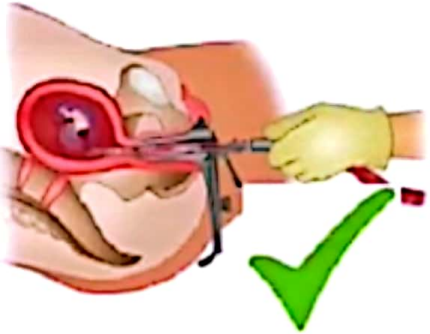

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- **Bedaquiline**
  - Weeks one to two: 400 mg once daily
  - Weeks 3 to 26/39*: 200 mg 3 times a week; plus

- **Pretomanid:** - 200 mg daily; plus

- **Linezolid:** - 600 mg once daily

- **Moxifloxacin**: - 400 mg once daily

*All patients above 14 years of age would receive the above standard dosage.

➢**There will be no weight bands**.

Pyridoxin should be added to prevent peripheral neuropathy

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IMPORTANT POINTS:

- If **Lzd 600** mg can't be continued, because of severe/ grade 03 toxicity, up to 09 weeks, the regimen is to be **declared as failed**

- The dose reduction of **Lzd to 300** mg, can be considered after 09 weeks, extending all the drugs till 39 weeks

- **Mfx** is a part of BPaLM regimen for **full course**, irrespective of resistance pattern to FQ at baseline or during the course of the regimen

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- The dose reduction of **Lzd to 300** mg, can be considered after 09 weeks, extending all the drugs till 39 weeks
- **Mfx** is a part of BPaLM regimen for **full course**, irrespective of resistance pattern to FQ at baseline or during the course of the regimen
- Since **Bdq** and **Lzd** resistance levels in India are low, the NTEG recommended that BPaLM regimen can be initiated in all the eligible MDR-TB patients irrespective of availability of baseline DST to these drugs

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## INCLUSION AND EXCLUSION CRITERIA

1. **Rifampicin resistance** detected.
2. MDR/RR-TB with **FQ resistance not detected**
3. **No history of exposure to previous treatment** with second-line medicines in the regimen (Bdq, Lfx, Cfz or Lzd as applicable) for more than one month (unless susceptibility to these medicines is confirmed)
4. **No extensive TB disease**
5. **No severe forms of extra-pulmonary** MDR TB like CNS TB, Spinal/ skeletal TB
6. **Non-pregnant , non lactating** pregnant women with <20 or < 24 weeks gestation and is willing for MTP, if **Eto** is considered in the regimen.

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OLD

| | |
|---|---|
| (4-6) Lfx Cfz Eto Z E $H^h$ (6-9) Bdq | (5) Lfx Cfz Z E |

NEW

| | |
|---|---|
| (2) Lzd (4-6) Lfx Cfz Z E $H^h$ (6-9) Bdq | (5) Lfx Cfz Z E |

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**Eto has been replaced by Lzd -**

- **Can be given to pregnant women,**
- **Thyroid function test** not required in pre-treatment evaluation.
- Can be given even in case of both **KatG & InhA mutations.**

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- Bdq (6 or 9 month) + Lfx Lzd Cfz Cs (18-20)

- In patients where **BPaLM** or 9-11 month **shorter oral** MDR/RR-TB regimen **can not be started**

- Repeat NAAT for **H, FQ, SLI, Eto** resistance detection or FL and SL LPA **(Lfx, Mfx, Am, Eto)** and LC DST **(Mfx 1.0, Lzd, Z, Bdq, Pa*, Dlm*)** (*whenever available) if culture is positive sent at the end of month six or any time beyond.

- For **XDR-TB** patients the duration of longer oral XDR-TB regimen would be for 20 months.

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- **All three Group A** agents and **at least one Group B agent** should be included to ensure that treatment starts with at least four TB agents likely to be effective and that at least three agents are included for rest of the treatment if Bdq is stopped

- If only one or two Group A agents are used, both Group B agents are to be included

- If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it

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# 6-9 months H mono/poly drug-resistant TB regimen

- **6-9 months**
- **Lfx R Z E**
- **No separate IP and CP.**
- Extensive disease, uncontrolled comorbidity, extra- pulmonary TB, if smear at the end of month 4 is found positive and when regimen is modified, the treatment may be directly **extended to 9 months**.

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Failing H mono/poly DR-TB regimen - **'probable MDR TB case':**

- BPaLM if eligible,
- 9-month shorter oral MDR/RR-TB regimen if eligible or
- longer oral M/ XDR-TB regimen.

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# DRUG RESISTANT TB

Date

## 6 month Regimen all oral

- Bedaquiline
- Pretomanid — BPaLM / BPaL
- Linezolid 600mg
- Moxifloxacin

### Indications

MDR/RR-TB (FQ susceptible)

Pre-extensively DR TB (FQ resistant)

Extensive PTB

Extrapulmonary TB (except CNS, miliary & osteoarticular TB)

HIV +ve

### CI

Extensively DR TB

Age <14y

Pregnant / Breast Feeding

Exposure to any of the drugs composing the regimen for >30days

Date

## 9 Month all-oral Regime

- Linezolid variation
- Ethionamide variation

**Intensive Phase**: (7) drugs

- Pyrazinamide
- FQ
- Bedaquiline
- High dose isoniazid
- Ethambutol
- Clofazimine
- Ethionamide (or linezolid 600mg OD)

For [4] months, Bedaquiline is given for 6months & linezolid is given for 2 months

* can be extended to 6 months if sputum tve at 4month

**Continuation Phase**: 4 drugs

- Pyrazinamide
- FQ
- Ethambutol
- Clofazimine

**Indications**

- MDR/RR TB (FQ susceptible)
- Extra pulmonary TB (except TB meningitis, miliary TB, pericardial TB, osteoarticular TB)
- Age < 14
- HIV +ve
- Ethionamide sparing regimen for pregnant & Breast feeding

Date _____

**CI**

- Pre-extensively DR TB
- XDR TB
- Extensive pulmonary TB
- Exposure to any of the drugs in the regimen for > 30 days.

* **FQs:** Moxi & Levo have similar efficacy for treating DR-TB, but Levo is preferred because Moxi is more cardiotoxic. but Levo causes MSK disorders in peds population.

**Longer Regimen (18-20 months)**

**Group A**
- Levo / Moxi
- Bedaquiline
- Linezolid

**Group B**
- clofazime
- cycloserine or Terizidone

**Group C**
Ethambutol, Pyrazinamide, Imipenem, meropenem, Delamanid
Amikacin (Streptomycin)
Ethionamide or Prothionamide, P-aminosalicylic ac

Bedaquiline & delamanid prolong QTc

Date

~~Must include~~

Intensive phase 4 drugs (3 from 'A' & 1 from 'B')

Continuation phase 3 drugs

Longer Regimen should be individualized based on DST & treatment history. when 4 likely effective drugs can't be obtained from group A/B, agents from group C are added

Indications

- XDR-TB
- When 6-m & 9m can't be used in MDR-TB, pre-extensive DR-TB Extensive PTB, Extrapulmonary TB (including TB meningitis, osteoarticular, pericardial, miliary TB)
- Lack of response or drug intolerance to shorter regimen drugs

# 3) Tuberculosis ( TB ) :

- **Personal History :**

Ahmed Mohammed Ali , 34 Y/O Saudi Male From Jazan , Policeman , Married For 10 Years And Has 3 Offsprings . Admitted Through ER On 12-1-1436 H .

- **C/O :**

Cough / 2 Months .

- **HPI :**

Patient's Condition Started About 2 Months Prior To Consultation , Non Productive Cough , Associated With Night Sweats And Intermittent Fever Usually In The Afternoon , Moderate Grade , Relieved By Taking Of Paracetamol . Two Days Prior To Admission The Patient Experienced Worsening Of The Condition , He Had Productive Cough Non-Bloody With Whitish Secretions . There Is Also Difficulty Of Breathing And Vomiting . The Patient Can't Eat Properly Because She Has No Appetite For Food . He Also Experience Stabbing Pain On His Chest Radiates To His Back . The Patient Only Took Paracetamol For His Fever . The Condition Associated With Loss Of Wright . The Is No Palpitation , No Cyanosis , No Wheeze .

- Systemic Review : -Ve .
- Hospital Course : Underwent CBC , Chest X-Ray , Oxygen , IV Fluids , Sputum Culture And The Patient Is Improving .

- **Past History :** -Ve .
- **Family History :** -Ve Apart From +Ve Consanguinity .
- **Social History :**

Good Living Conditions & Socio-Economic Status .

No Special Habits Of Medical Importance .

- **Drugs & Allergies :** -Ve .

**Summary**

34 Y/O Saudi Male Admitted Through ER Complaining Of Productive Cough / 2 Months Non-Bloody, Which Associated With Moderate Fever , Weight Loss , Chest Pain And Difficulty In Breathing .

**+Ve Findings In Examination :**

- **General Examination :** Looking Ill , Feverish , Underweight .
- **Local ( Respiratory ) Examination :**
  - ✓ **Inspection :** The Right Side Moving Less Than Left .
  - ✓ **Palpation :** The Chest Expansion Less Than Normal .
  - ✓ **Percussion :** Dullness On Right Side , Increase TVF .
  - ✓ **Auscultation :** Crepitations .

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